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14. ABSTRACT Three areas emerged where the PTSD/mTBI participants showed strengths in executive control functions: (1) overriding conflicting response cues in a flanker task, (2) overcoming proactive interference in working memory (suppressing material that is no longer relevant), and (3) stopping a motor response that was already planned. These strengths are closely related to other executive functions that were weaker in the PTSD/mTBI participants. They showed pronounced deficits in (1) motor response inhibition, (2) consistency in responding, and (3) control over emotional reactions to trauma reminders. Although they were not uniformly impaired in multitasking, the patients showed behavioral and electrophysiological deficits in working memory retrieval that became apparent only when they performed a secondary task during the delay interval. Ultimately, these types of dissociations are informative for demonstrating that PTSD/mTBI can spare some important cognitive abilities. These strengths could be exploited in future developments of psychotherapy and cognitive rehabilitation techniques.					
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INTRODUCTION: Combat veterans who have sustained a traumatic brain injury (TBI) can show impairments in behavioral and cognitive control and increases in impulsivity. In addition, many with mild TBI will also have post-traumatic stress disorder (PTSD). To improve diagnostic capabilities and better define treatment alternatives, it is important to determine the unique (and shared) contributions of each disorder to deficits in cognitive function and emotional control. Three specific control functions are being targeted: (1) **resolving conflict** between competing responses and competing aspects of a visual display; (2) **monitoring for errors** in performance and adjusting behavior accordingly; (3) **multi-tasking**, or the ability to maintain adequate performance in dual task situations. Converging evidence is obtained through the combined use of behavioral testing, electrophysiological recording (event-related potentials, ERPs), and structural imaging (diffusion tensor imaging, DTI). The project applies innovative methods by expanding the application of ERPs into the cognitive and behavioral domains most troublesome for patients with TBI and PTSD.

BODY: The research accomplishments associated with each task outlined in the approved Statement of Work are summarized below.

Project Timeline and Milestones					
	Year 1	Year 2	Year 3	Year 4	totals
Patient Recruitment					
Civilian Controls	1	10	14	6	31 (3)
Military Controls	3	15	12	4	34 (2)
mTBI Patients	0	1	0	2	3 (1)
PTSD Patients	4	4	0	3	11 (1)
mTBI + PTSD	13	9	4	8	34 (3)
Pilot Studies	Exp. 1-2	Exp. 4	Exp. 4	Exp. 3	
Behavioral Testing	Exp. 1	Exp. 1	Exp. 1	Exp. 1	
ERP Testing		Exp. 2	Exps. 2, 4	Exp. 3, 4	
Integrative Analysis		ongoing	ongoing	ongoing	

Note: In the **totals** column, the number in parentheses indicates the number of individuals who had to be excluded after enrollment, once an exclusionary criterion was discovered. They are **not** included in the “total” figure to the left.

Phase 1: Patient Recruitment:

In the fourth year of the project, we recruited 6 civilian controls, 4 military controls, and 13 patients. Of the patients, there were 2 mTBI only, 3 PTSD only, and 8 with mTBI + PTSD. Not included in these totals were 2 patients excluded after enrollment (1 patient was not OEF/OIF; 1 patient had other medical issues).

Our original goal was to recruit 40 participants in each of the three patient groups. We came closest to meeting this goal for the combined mTBI + PTSD group. We were unsuccessful in recruiting a cohort of mTBI patients without PTSD. This issue has affected all investigators working with similar groups of OIF/OEF Veterans, and the high level of co-morbidity became more apparent over the course of the project. Over four years, our observations were that most of the patients who meet the selection criteria for mTBI also have a formal PTSD diagnosis. Therefore, it was necessary to drop this group from the project. In our experience, these

individuals might show better recovery from post-concussive symptoms (PCS) and hence do not show up at neurology or mental health clinics, or else they may not receive their health care from the VA.

Nonetheless, we were able to make meaningful comparisons between the mTBI+ PTSD and PTSD-only groups in some of the studies, as outlined in Phase 3 below. Our results agree with an increasing number of studies revealing that PTSD makes a substantial contribution to the persistent PCS and cognitive problems reported by OEF/OIF Veterans (Hoge et al., 2008; Lippa et al., 2010; Polusny et al., 2011).

Phase 2: Pilot Studies:

(A) Experiment 3 – Performance Monitoring and Motivational Significance:

Background: Exp. 3 investigates the role of motivation and task engagement on the neural activity associated with performance monitoring and the evaluation of feedback. It also assesses the participants' propensity to engage in impulsive choices and their level of reward-sensitivity. A specific EEG component, called the feedback negativity (FN), has been interpreted as reflecting an error in reward prediction (Miltner et al., 1997; Gehring & Willoughby, 2002). The neural generator of the FN is thought to be located in the medial frontal cortex, which is involved in processing feedback signals. This study pursues the questions of whether PTSD/mTBI patients will show a normal FN response to performance feedback in a blackjack task (e.g., win or loss), and the degree to which the electrophysiological response is sensitive to reward magnitude.

Design: The experiment consists of computer simulated game of blackjack that is realistic, with the participant playing against a “dealer” and making decisions on whether to “stay” or “hit” (draw another card). If the player beats the dealer, they win the hand and gain a financial reward. If they lose the hand to the dealer or “bust” (go over 21), they pay a penalty. All participants start with a set sum of money with which they may gamble. To increase motivation, participants will receive the monetary earnings at the end of the game; however, no participant is required to pay if they end up in the red. EEG analyses initially focus on the responses to positive feedback (wins) and negative feedback (losses). In addition, responses to negative and positive feedback displays following high-risk choices (e.g., dealt two cards that sum 18, draw another card) will be compared to those following low-risk choices (e.g., dealt two cards that sum 14, draw another card).

Results: Preliminary results in 15 civilian controls revealed an FN component at 300 msec that is larger to feedback indicating a loss, rather than a gain (Fig. 1, next page). The expected results were obtained, and future studies will be conducted using this design in PTSD/mTBI patients and age-matched military controls.

Significance: We predict that individuals with mTBI (with or without PTSD) will show reductions in FN amplitude, specifically in relation to negative feedback following high-risk decisions. This would suggest that normal function of the orbitofrontal cortex is compromised, based on ERP findings showing error monitoring deficits in severe TBI patients (Turken & Swick, 2008), and on prior studies of impulsive choice (Dalley et al., 2011). Results from this experiment will have important implications for evaluating real-life changes that can occur after TBI, such as increases in impulsive behaviors, including addictions and problematic gambling.

Gambling Task - Response to Feedback

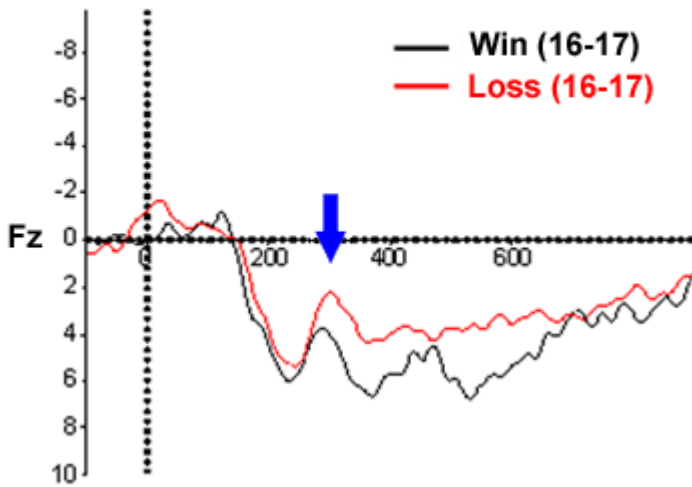


Fig. 1 – Event-Related Potentials to Feedback in the Gambling Task. ERPs were recorded from 15 civilian controls, time-locked to the onset of feedback indicating whether they won or lost the hand. Here, ERPs from frontal midline electrode Fz are averaged across winning or losing hands of 16 and 17. The feedback negativity (FN) is indicated by the blue arrow. Negative is plotted upwards.

(B) Structural MRI: Progress in collecting structural MRI data was hampered by the fact that the 1.5 T Phillips scanner at Martinez was taken out of service on approximately half way through the project and replaced with a 3 T Siemens Verio scanner. Developing new pulse sequences and establishing other research protocols took a number of months, so the new scanner was not operational until recently. However, structural MRI data from 8 patients and 8 controls were obtained with the 1.5 T scanner by our colleagues, research neuroimaging director Dr. David Woods, physicist Dr. XJ Kang, and statistician Timothy Heron. Unfortunately, we were not able to do structure/function correlations with this low n , but preliminary pilot data are presented below. This initial phase applied multimodal surface-based morphometry to precisely measure the area, thickness, and tissue properties of the anterior cingulate gyrus, a region implicated in error monitoring (see Exp. 2). No differences between groups in were observed in midline cingulate regions (Fig. 2, next page).

DTI studies thus far have yielded mixed results in veterans with mTBI due to blast. One report failed to detect differences in the brains of OEF/OIF Veterans with mild to moderate TBI (Levin et al., 2010). Another study in military personnel with more “severe” mTBIs (from a combination of blast injury and secondary head trauma), i.e., the group of U.S. military personnel airlifted to Landstuhl Medical Center in Germany, did show evidence of white matter abnormalities on DTI scans (Mac Donald et al., 2011). However, a new paper by Bazarian et al. (2012) found that DTI measures were not related to mTBI diagnosis in a group of 52 OEF/OIF Veterans. Therefore, it is important to pursue research with other imaging modalities to find reliable biomarkers of blast injury.

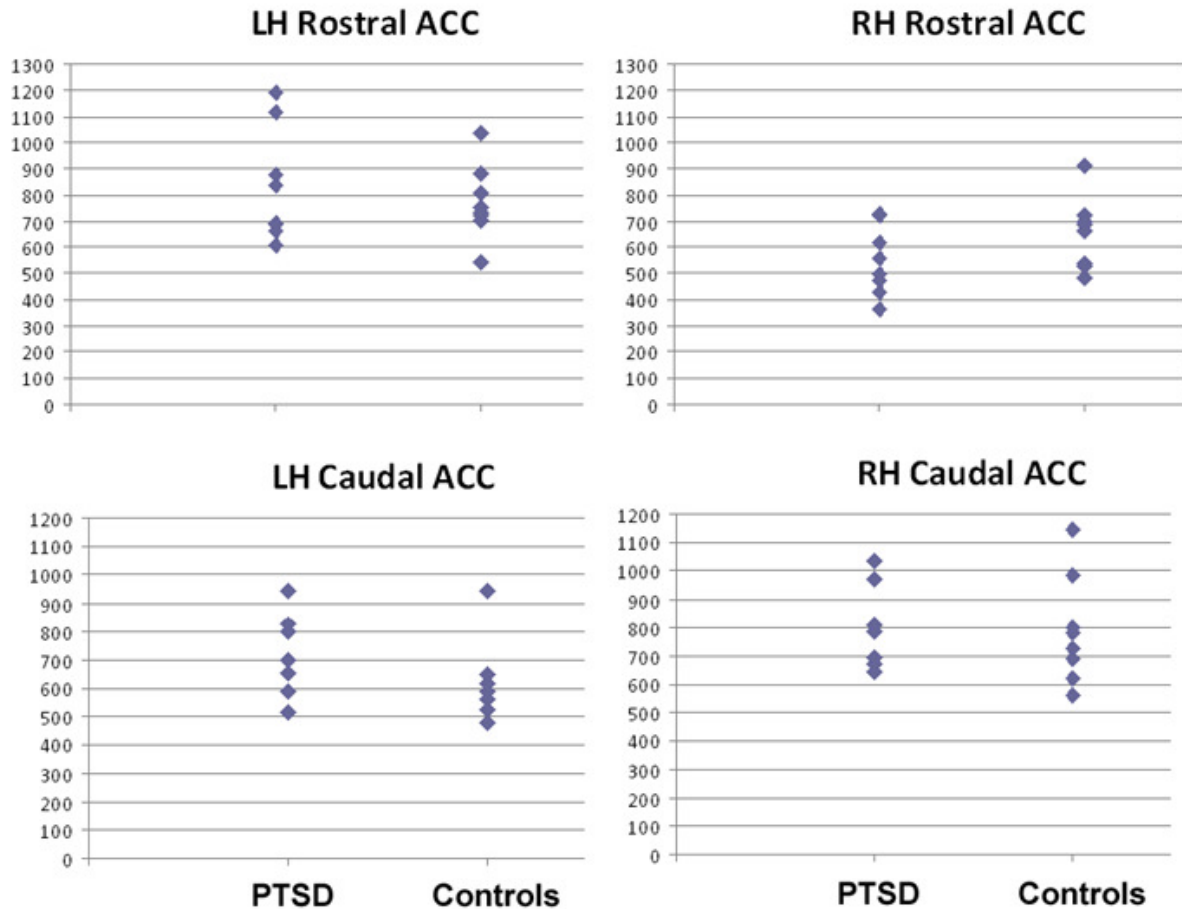


Fig. 2 – Surface-Based Multimodal Morphometry. Area measurements from the rostral and caudal anterior cingulate cortices of patients with PTSD and age-matched military control participants. LH = left hemisphere, RH = right hemisphere.

Phase 3: Behavioral Testing:

Two publications have resulted from this phase of the project in Year 4, with others in preparation. A manuscript describing results from the emotional Stroop task (Exp. 1) is attached as Appendix 1 (Ashley et al., submitted). Results from the Go/NoGo (GNG) task, another executive control task that provides a measure of response inhibition, have been published (Swick et al., 2012; Appendix 2). Brief summaries are provided below, along with detailed results from related studies. Abstracts from conferences are included as Appendices where appropriate.

(A) Experiment 1: Emotional Stroop task with Combat-Related Words (Appendix 1):

This experiment was designed to be an objective behavioral measure that may be able to distinguish between combat Veterans with a PTSD diagnosis and those without. The participants were 30 PTSD patients, 30 military controls, and 30 civilian controls. Words were presented in blocks of negative emotional words, positive emotional words, combat-related words (specific to OEF/OIF), and appropriately matched neutral words. The metric of interest was the emotional Stroop effect, or slowing of reaction times (RTs) for naming the color of combat words relative to neutral words. Trauma-relevant material is thought to divert attention away from the primary

task in those with PTSD. The emotional Stroop effect was nearly three times larger in the patient group (112 msec) than that seen in the military control participants (41 msec). There were also significant correlations between the size of the combat Stroop effect and scores on the PTSD Checklist-Military (PCL-M). Thus, the emotional Stroop task shows promise as an objective indicator of PTSD symptomology suitable for use as an outcome measure in PTSD intervention studies (Ashley et al., submitted). We have made our stimulus list available as an Appendix of the manuscript, which will appear in the article when it is published.

(B) Go/NoGo Task – Motor Response Inhibition (Appendix 2):

This task measures a person's ability to inhibit an inappropriate response. Single letters were rapidly presented on a computer screen, and subjects were instructed to respond as quickly as possible to any letter except "X," the NoGo stimulus. The difficulty of the task was manipulated by altering the probability of "NoGo" trials relative to "Go" trials, i.e., 50% NoGo (easy) vs. 10% NoGo (hard). Performance measures from the patient group (n=40) were compared to those from an age-matched Veteran control group (n=33). The patients were significantly impaired on this task overall, committing more errors in both conditions ($p<.0001$). Furthermore, "Go" probability interacted with group ($p<.003$), reflecting an exacerbated deficit in the hard condition. Veterans with mTBI+PTSD did not make more mistakes on this task than Veterans with PTSD only, suggesting that an additional mTBI(s) did not compound the response inhibition deficit associated with PTSD (Swick et al., 2012).

(C) Response Variability (Swick et al., in preparation):

Another aspect of executive functioning is control over response variability. Consistency in behavioral responding is required for the efficient performance of many cognitive tasks. Often measured as trial-to-trial variability in RT, intra-individual variability indexes the stability of executive control processes over time (West et al., 2002). A high level of response variability has been characterized as a marker of executive dysfunction and inhibitory inefficiency, cognitive instability, and mental noise. Specific regions of the prefrontal cortex (PFC) have been associated with this aspect of cognitive control (Stuss et al., 2003). Here, the RT variability seen in the GNG task was analyzed for 34 controls and 45 PTSD patients.

A measure of RT variability on Go trials, the intra-individual coefficient of variation (ICV), was obtained from the formula, Standard Deviation/mean RT (Stuss et al., 2003). The ICV ratio is a standard measure designed to correct for differences in group RTs. Statistical analysis indicated that the patients showed greater response variability than controls [$F(1,77)=12.38$, $p=.0007$]. RTs were more variable in the 90/10 condition than the 50/50 condition for all participants ($p<.0001$). Furthermore, condition interacted with group [$F(1,77)=7.27$, $p=.007$], suggesting that the patients were disproportionately impaired in the difficult 90/10 condition. Because raw RTs did not differ between the groups (controls: 379 ms and patients: 370 ms, $p=.6$), a secondary ANOVA entered SD values instead of the ratio. A main effect of group was still observed [$F(1,77)=6.12$, $p=.02$], with patients more variable than controls (95 ms vs. 73 ms). Next, the relationship between RT variability and error rate was examined. The correlation between response variability and false alarm errors was significant for both the 50/50 ($r=.56$, $p<.0001$) and the 90/10 conditions ($r=.49$, $p<.0001$), suggesting that more variable RTs were associated with a greater propensity for impulsive errors.

Despite having mean RTs that were indistinguishable from controls, the patients had greater variability in their response times. More variable RTs were in turn associated with a greater

number of errors, replicating previous findings (Bellgrove et al., 2004). Increased response variability has also been observed in children with ADHD (Suskauer et al., 2008), and is viewed as another facet of their response inhibition impairments. Stuss et al. (2003) has suggested that an alteration in the consistency of task performance could contribute to the PFC patients' difficulties in everyday life. Likewise, the combination of inconsistent performance and impaired response inhibition shown by the veterans with PTSD/mTBI could have deleterious effects on daily activities requiring these cognitive control functions, such as driving (Lew et al., 2010) and multitasking (see Phase 4, Part C below).

(D) Impaired identification of facial expressions of fear in Iraq war veterans with PTSD and mTBI (Appendix 4): Ashley, Larsen, Pratt, & Swick, 2012 Cog Neurosci Society Meeting.

In this study, we attempted to replicate the findings of Poljac et al. (2011), who found accuracy impairments and decreased sensitivity in recognizing expressions of fear and sadness in war veterans with PTSD. We also predicted that PTSD patients would interpret ambiguous expressions as angry due to the hypervigilance for threats that is characteristic of PTSD. We expected that all subjects would make classic misattribution errors, such as mistaking Surprise for Fear, and Anger for Disgust. Initial results suggested a reduced ability to recognize lower intensity fearful expressions in the patients, but no effect on recognizing sadness.

Phase 4: ERP Studies:

In Year 4, we updated the analyses from the error monitoring study (Exp. 2). We analyzed ERP and behavioral data from the dual task/flanker study (Exp. 4). We also prepared the draft of a manuscript on the dual task/working memory study (another aspect of Exp. 4) that describes results from mTBI/PTSD patients and military controls (Appendix 3; Honzel et al., in preparation). To better understand the nature of the working memory problems exhibited by the patients, we have initiated new analyses of EEG activity during the memory retention interval. Findings from other experiments are also discussed below.

(A) Experiment 2 – Error Monitoring

The error-related negativity (ERN) is an ERP component generated when subjects make errors in speeded reaction time tasks (Gehring et al., 1993). This component is considered to be an on-line index of performance monitoring that reflects neural activity in the medial prefrontal cortex. Lesion evidence suggests that a major generator of the ERN is located in the dorsal anterior cingulate cortex (Swick & Turken, 2002). Initially, we reported that PTSD patients and controls showed a significant reduction in ERN amplitude, but this was no longer the case after additional subjects were run. One issue was that several of the participants performed the task incorrectly on some of the trials due to a misinterpretation of the instructions, but didn't realize it. This would negate ERN generation on those trials, because awareness of error is a crucial part of the neurophysiological response.

Fig. 3 (next page) shows the averaged ERPs from 10 controls and 10 participants with PTSD+mTBI on incorrect trials in a difficult attention task. The amplitude of the ERN tended to be smaller in the patients at central and posterior electrodes, but this difference did not reach significance. Prior experiments with TBI patients have focused on those with severe injuries, and those studies have reported large ERN decreases (Larson et al., 2007; Turken & Swick, 2008). The present results also differ from the enhanced ERN responses observed in populations with other anxiety disorders (generalized anxiety disorder, OCD). It is possible that mTBI and PTSD

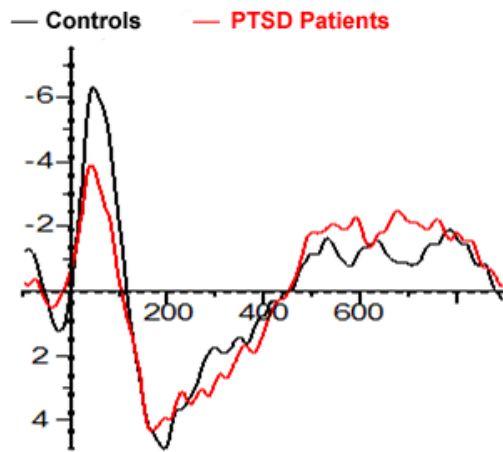


Fig. 3 – The error-related negativity (ERN) component on error trials, recorded from the subset of controls (n=10) and patients (n=10) who correctly performed the task. These ERPs (from central midline electrode Cz) were time-locked to response onset (at the vertical marker). Negative is plotted upwards.

are acting in opposition, and that depression plays a moderating role. A precedent for this was observed in a recent paper by Weinberg et al. (2012). Relative to controls, ERN was increased in participants with generalized anxiety disorder, but not in those with comorbid anxiety and major depression. The relationship between mTBI, PTSD, depression, and ACC function is complicated. In the future, studies that combine ERPs and MRI in larger groups of patients will be informative, and this is an area of research that Dr. Honzel (Pratt) wishes to pursue.

(B) Experiment 4 – Dual Task Performance in the Flanker Task:

Background: This study examined the effects of multi-tasking on behavioral performance and brain activity during an attention task. Working memory and attention interact in a way that allows us to focus on relevant items and maintain current goals. Multi-tasking increases the demands on working memory and reduces the amount of resources available for cognitive control functions. If veterans with PTSD/mTBI have to rely on the recruitment of cognitive resources to a greater extent than controls, then their performance may suffer disproportionately while multi-tasking. Results from civilian controls have been published (Pratt et al., 2011).

Design: The experimental design is a modification of that study, as shown below in Fig. 4. The flanker task was performed alone (single task) or concurrently with a Sternberg working memory task (dual task). In the Sternberg task, a set of 1 or 4 consonants was presented. In the single task version, the letter(s) were to be remembered during an unfilled 8.5 second delay. In the dual task version, 9 trials of the flanker task intervened during the delay.

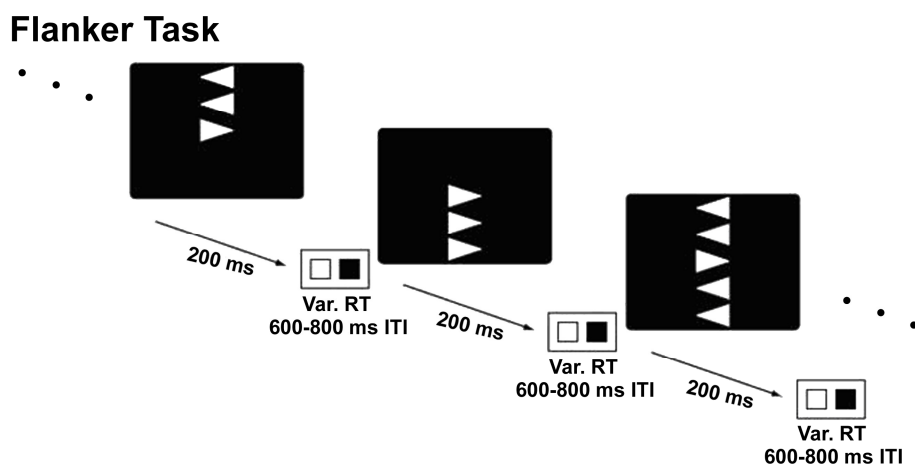


Fig. 4 - Flanker Task Design (Pratt et al., 2011). Participants responded to direction of the central arrow using a two-button response. Flanker arrows could be either congruent or incongruent and above, below or both above and below the central arrow. In the dual task condition, participants were shown a set of 1 or 4 letters to remember at the beginning of the trial, performed the flanker task during the delay interval, then were shown a probe letter that either was or was not presented in the previous memory set.

Behavioral Results: In the flanker task, subjects are generally slower and less accurate on trials in which the flanker arrows are incongruent relative to the target arrow (Eriksen & Eriksen, 1974). These classic flanker interference effects were observed in the present study. All participants were 50-60 msec slower for incongruent than for congruent trials. Interestingly, veterans with PTSD/mTBI performed as well as controls on both the single task and dual task versions of the flanker. This was true for both accuracy (Fig. 5) and reaction times.

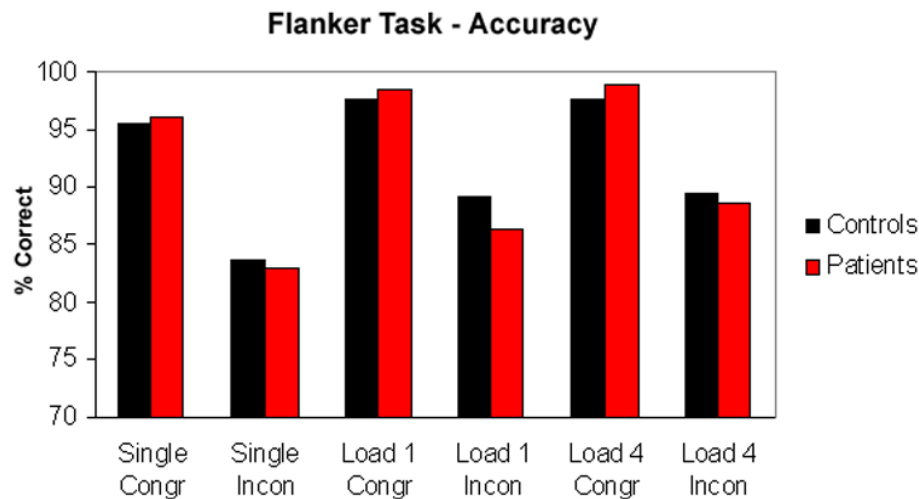


Fig. 5 - Accuracy on the Flanker Task. Percentage of correct trials is shown for all six conditions in the mTBI/PTSD patients and matched military controls. All participants were less accurate on trials when flankers were Incongruent to the target, relative to Congruent trials. Unexpectedly, all subjects performed worse in the single task condition. However, the patients were just as accurate as controls for all conditions. **Single Congr** = Single task flanker, Congruent trials; **Single Incon** = Single task flanker, Incongruent trials; **Load 1 Congr** = Dual task flanker, Load 1, Congruent trials; **Load 1 Incon** = Dual task flanker, Load 1, Incongruent trials; **Load 4 Congr** = Dual task flanker, Load 4, Congruent trials; **Load 4 Incon** = Dual task flanker, Load 4, Incongruent trials.

ERP Results: We also recorded event-related potentials (ERPs) during both the single and dual task conditions. Fig. 6 illustrates that the patients showed more positive-going potentials than controls over the prefrontal cortex, starting from 200-300 msec post-stimulus. This might indicate that a greater degree of effort was expended by the patients in performing the tasks, although this interpretation is still speculative. EEG data analysis in this aspect of Exp. 4 is ongoing.

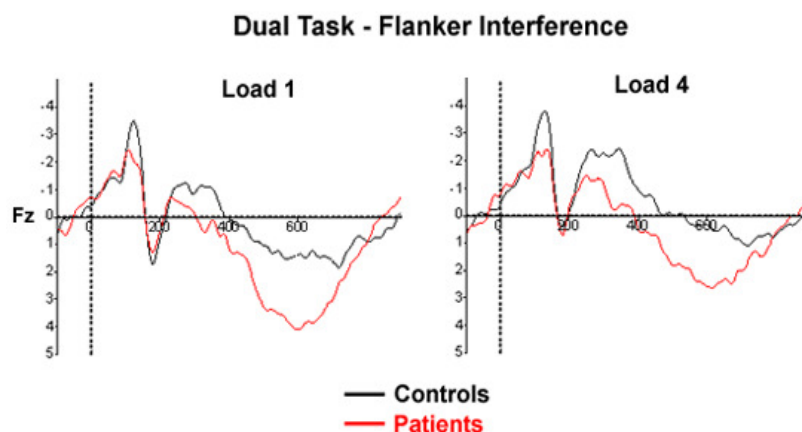


Fig. 6 – Event-Related Potentials to Incongruent Flankers. ERPs were recorded from 13 Control Veterans and 13 Veterans with PTSD/mTBI in the dual task flanker. These ERPs (from frontal midline electrode Fz) were time-locked to stimulus onset (at the vertical marker). Controls are in black, Patients are in red. Negative is plotted upwards.

Significance: The patients' intact performance in a demanding attention task suggests that some forms of executive control are spared in OEF/OIF veterans with PTSD/mTBI. However, they did have problems with the working memory component of the task, especially when combined with the flanker (summarized below). This may have implications for the successful completion of everyday activities.

(C) Experiment 4 – Dual Task Performance in the Sternberg Memory Task (Appendix 3):

Background: This aspect of Exp. 4 set out to determine if the working memory (WM) impairments observed in previous studies of PTSD (e.g., Bremner et al., 1993) can be linked to executive control limitations. Here we examined ERPs and behavioral performance on the Sternberg WM task alone and when the flanker interference task was performed during the maintenance period. Reduced accuracy on the WM task only under difficult conditions could suggest dysfunction in the central executive component of WM (Baddeley, 1996), rather than a general decline in remembering information across a short delay.

Behavioral Results: In contrast to their intact performance on the flanker task, the patients were less accurate than controls on the Sternberg working memory task, and their performance suffered to a greater extent in the dual task than in the single task version (Fig. 7). This was supported by a main effect of group ($p=.03$) and a group by task interaction ($p=.04$). The patients showed a trend for worse performance in the single task Sternberg ($p=.12$) but were significantly less accurate than controls on the dual task Sternberg ($p=.02$), when the demanding flanker task occurred during the working memory delay.

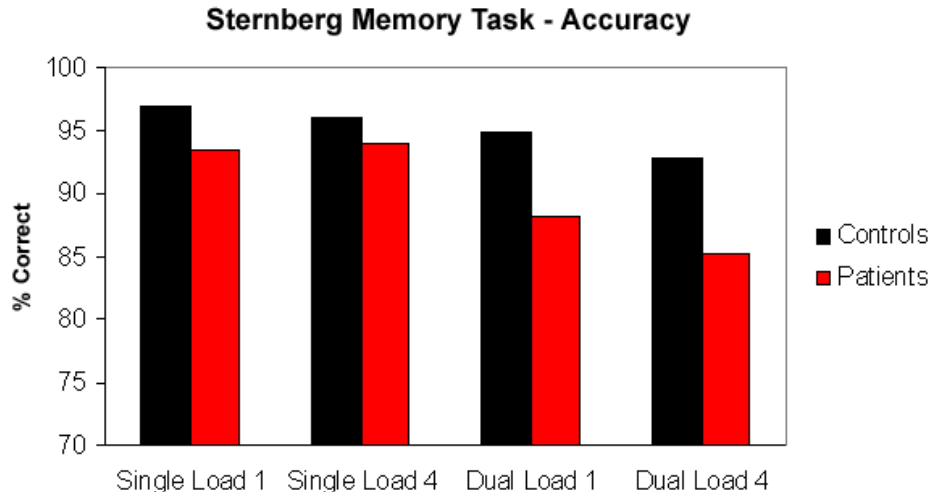


Fig. 7 - Accuracy on the Sternberg Working Memory Task. Percentage of correct trials is shown for all four conditions in the mTBI/PTSD patients and matched military controls. Patients were less accurate than controls overall, to a greater extent in the dual task condition. **Single Load 1** = Single task Sternberg, Load 1; **Single Load 4** = Single task Sternberg, Load 4; **Dual Load 1** = Dual task Sternberg, Load 1; **Dual Load 4** = Dual task Sternberg, Load 4.

ERP Results: The PTSD patients showed a reduction in the electrophysiological correlate of working memory retrieval in the dual task condition only. This ERP response, the old/new effect, differentiates correctly recognized old items from correctly rejected new items, beginning at 300 ms post-stimulus and continuing for several hundred milliseconds. The ERP old/new effect was

intact in the single task version of the Sternberg, suggesting that the neural processes underlying working memory retrieval were spared when distraction was minimized (Appendix 3, Honzel et al., in preparation).

Significance: These findings suggest that working memory performance is compromised in OEF/OIF veterans with PTSD/mTBI when additional cognitive demands require multitasking. Conversely, performance on the secondary visual attention task was not impaired in the patients. Responding quickly and correctly on incongruent flanker trials requires one to override automatic response tendencies. This form of executive control was intact in the PTSD/mTBI group, unlike the impairments that were seen in response inhibition (Go/NoGo task) and emotional control (emotional Stroop task). These types of dissociations are informative for theoretical models of executive control function (Miyake et al., 2000), as well as for demonstrating that PTSD/mTBI can spare some important cognitive abilities.

(D) Experiment 4 – ERP and EEG Spectral Analyses During Memory Encoding and Retention:

Because of the behavioral and neurophysiological deficits shown by the patients during the memory retrieval phase, it is important to determine whether there are also weaknesses during the memory encoding and delay intervals. To better understand the nature of the multitasking problem exhibited by the patients, we have initiated new analyses of EEG activity during the encoding and delay period of the Sternberg memory task, considering the effects of both set size (i.e., whether participants are maintaining one letter or four letters in working memory) and of task (i.e., whether participants are maintaining the letters with no distraction or performing the secondary flanker task during the delay). In addition to performing an ERP analysis time-locked to encoding, we are also analyzing the data in the frequency domain on a second-by-second basis as the participants encode the stimuli to be remembered and maintain them during the delay. The focus is on EEG activity in the theta (~3-7 Hz) and alpha (~7-13 Hz) bands (e.g., Khader et al., 2010).

Ongoing ERP analyses at encoding suggest interactions between set size, task, and group ($p=.02$). Once the array of letters to be remembered has been presented for 500 ms, only the individuals with PTSD demonstrate a significant effect of set size (1 vs. 4 letters), and only if the secondary flanker task is about to begin during the maintenance interval. This set-size differentiation at encoding is not obtained for the PTSD patients in the single task, nor for the controls in either condition. These data might suggest that control participants are well within the capacity limits of working memory at encoding, regardless of whether the set size is 1 or 4, and regardless of whether the secondary flanker task is beginning to divert cognitive resources. Individuals with PTSD, however, may be within working memory capacity only for the single task condition, in which they can maintain the letters without additional distraction. With an impending flanker task, limited cognitive resources would seem to be diverted away from the Sternberg letters at encoding.

A preliminary frequency-domain analyses using a fast Fourier transform is suggestive of spectral differences between the controls and PTSD patients, even as the Sternberg letters are being encoded (Fig. 8, next page). Specifically, power values in the theta and alpha bands tend to be larger in the dual-task condition than the single-task condition, and tend to be larger for control participants than the PTSD participants. These differences seem particularly prominent in a 1000-2000 ms window defined relative to the onset of the Sternberg memory set.

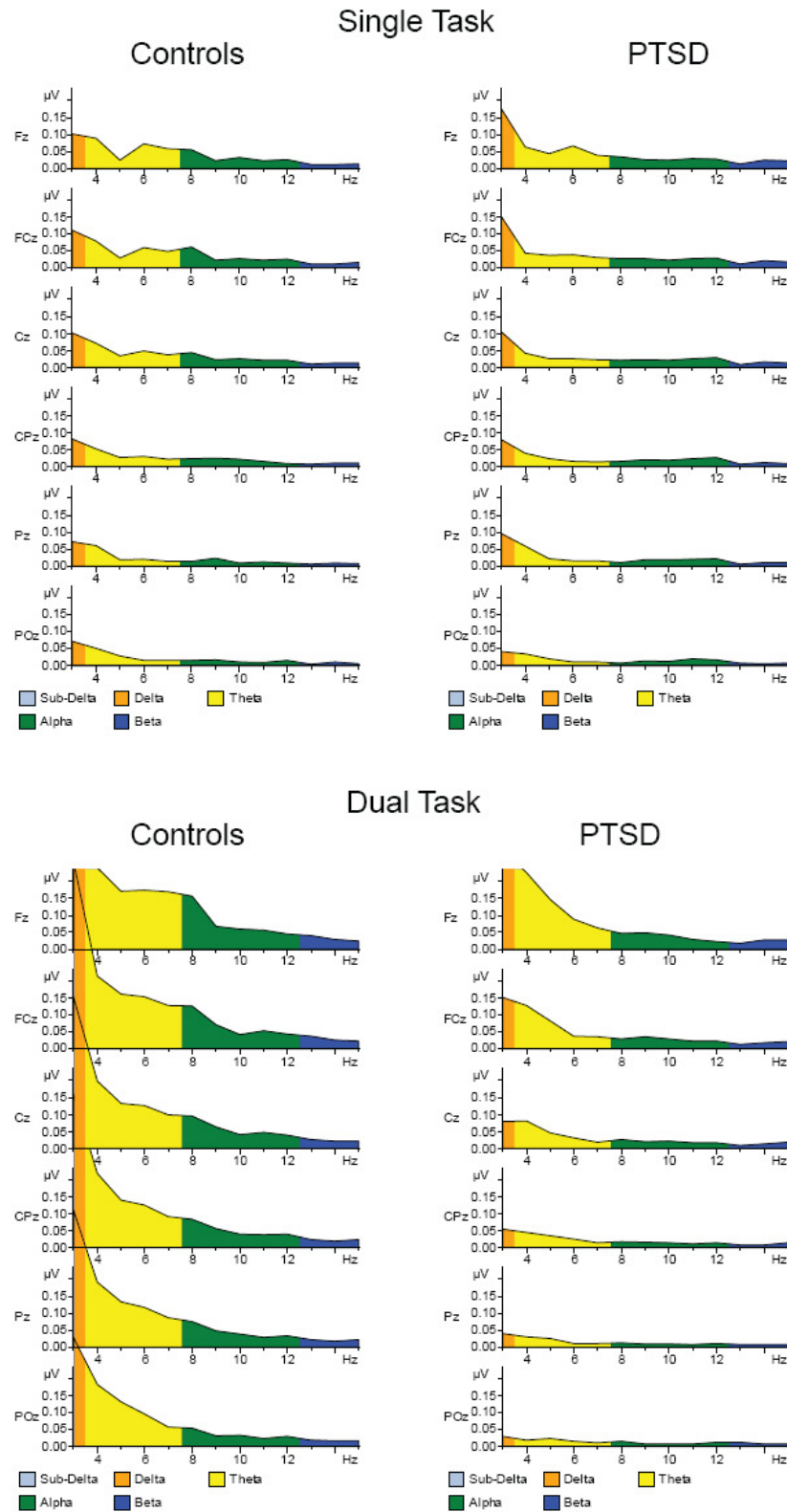


Fig. 8 – EEG Spectral Analysis During Encoding of the Memory Set. Fast Fourier Transform was applied to the EEG data during the 1000-2000 ms post-stimulus interval, when participants were encoding the set of letters to be remembered across a short delay. Note the reduction in theta and alpha power in the PTSD patients during the dual task condition.

(E) Working Memory for Verbal and Visual Material:

Background: This study is a further exploration of working memory abilities in the OEF/OIF population. Other researchers have reported WM impairments in PTSD patients when non-emotional material was used (Bremner et al., 1993), and we observed a verbal WM deficit in the previous study when executive processing resources were taxed. However, there is a debate as to whether verbal working memory (and verbal memory more generally) might be impaired to a greater extent than visual memory (Brewin et al., 2007).

Design: The experimental design adopted the item recognition task of Thompson-Schill et al. (2002), but used words and visual patterns (instead of letters) as the stimulus material. Participants were required to judge whether a test probe item was a member of a set of studied items. At the beginning of each trial, a “Get Ready” cue was presented for 1,000 msec. This was followed by a cross in the center of the screen. After 500 msec, the target set was presented. The target set was a visual display of four words or visual patterns arranged above, below, to the left, and to the right of a central fixation cross. The target set remained on the screen for 1,500 msec, followed by a 3,000-msec delay. Following this delay, the probe (i.e., a single word or pattern) appeared in the central location, and the subject was instructed to indicate whether that probe was a member of the current target set or not. Proactive interference (intrusions of previously studied, but now irrelevant stimuli) was examined as well.

Results: All participants were much better at remembering verbal than visual (nonverbal) stimuli ($p < .0001$), despite our efforts to match the stimulus sets for difficulty. The patients made significantly more errors than controls ($p = .01$), and this pattern was similar for both verbal and nonverbal items ($p = .59$; see Fig. 9). Thus, the hypothesis of selective impairment in verbal working memory was not supported.

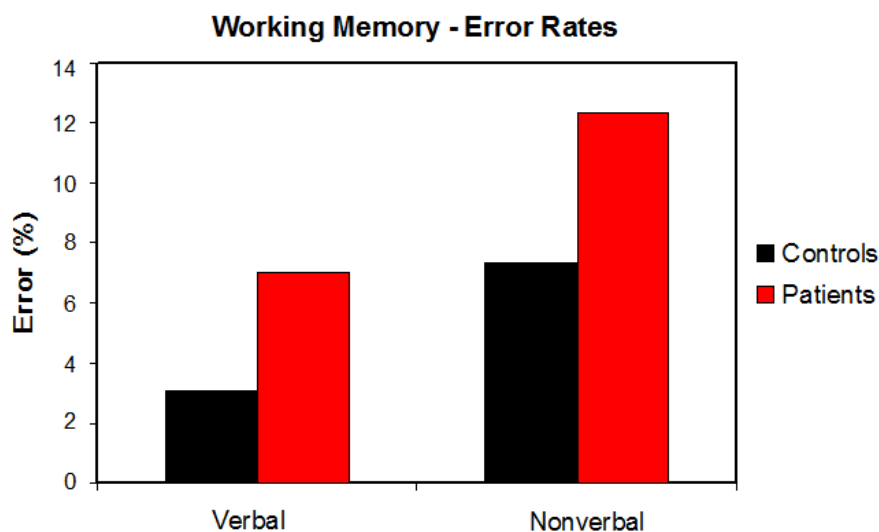


Fig. 9 – Error Rates in the Working Memory Task. Percentage of incorrect trials for 16 Control Veterans and 18 Veterans with PTSD \pm mTBI. The patients were impaired to a similar extent for both verbal and nonverbal stimuli. Controls are in black, Patients are in red.

Conversely, proactive interference (measured as RT slowing) was unexpectedly *lower* in the PTSD/mTBI patients ($p = .07$), although this was only a trend (see Fig. 10, next page). It appeared that the reduction was larger for nonverbal material, but the interaction with group was not significant ($p = .12$).

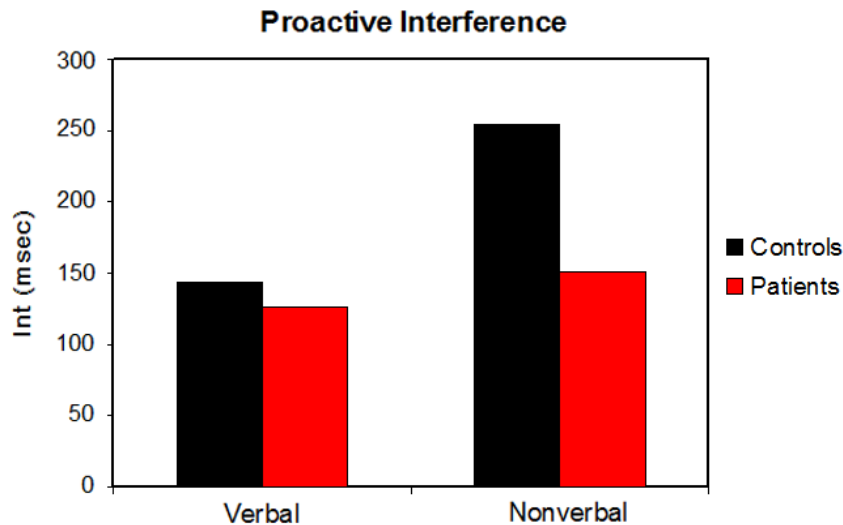


Fig. 10 – Proactive Interference for RTs in the Working Memory Task. RT slowing (in msec) for 16 Control Veterans and 18 Veterans with PTSD \pm mTBI. The patients tended to show less interference from previously encoded but now irrelevant items. Controls are in black, Patients are in red.

Significance: The ability to suppress proactive interference is thought to require executive control processes in the prefrontal cortex (Thompson-Schill et al., 2002). The patients with PTSD were unexpectedly better at this, which could indicate either (1) Weaker encoding of the studied items led to fewer subsequent intrusions and less interference; or (2) the PTSD patients were able to better suppress stimuli that were no longer relevant, which would be an important observation for the management of flashbacks and other disturbing memories. This interpretation should be made cautiously, however, since the difference between groups was not significant. Nonetheless, future studies that use emotional and trauma-relevant material within this design would be informative.

Phase 5: Integrative Analysis and Presentation of Findings at Scientific Meetings and Publication in Scientific Journals

During this reporting period, we published one manuscript, submitted another for publication, and prepared a draft version of a third that will soon be submitted for publication. We also presented results at one internationally known conference. During the proposed no-cost extension period, we anticipate writing three more journal articles to be submitted for publication.

Ongoing analyses are examining the relationship of the participants' self-reported impulsivity on the Barratt Impulsiveness Scale (Patton et al., 1995) and the UPPS-P Impulsive Behavior Scale (Cyders et al., 2007) to PTSD symptoms, behavioral performance, and ERP components. Comparison of performance across tasks will allow a more integrated view of the cognitive strengths and weaknesses shown by OEF/OIF veterans.

Finally, we have initiated a new set of analyses to examine the spectral properties of EEG activity associated with remembering a set of letters across a delay interval. Combined with additional examination of ERPs during memory encoding, this will provide a more complete picture of the neural correlates of working memory, the recruitment of additional resources during multitasking, and how these processes go awry in PTSD/mTBI patients.

KEY RESEARCH ACCOMPLISHMENTS:

- Demonstrated that the emotional Stroop task with combat-related words is a robust and sensitive measure of attentional bias to trauma-relevant material in OEF/OIF Veterans with PTSD. The enhancement of the emotional Stroop interference effect was specific for combat words, as it did not occur for general negatively-valenced words, and it correlated most strongly with the re-experiencing subscale of the PCL-M.
- Determined that the PTSD patients showed a trend for a different pattern of habituation to combat words than the controls: they did show some habituation (but not until the final quarter of the block), but the interference effect remained significant.
- Our carefully matched stimulus lists will be published along with the manuscript describing these results (Ashley et al., submitted). This task may serve as a useful pre- and post-treatment measure in intervention studies with veterans with PTSD.
- Published a paper reporting that OEF/OIF Veterans with PTSD were impaired in a Go/NoGo task that measures the ability to inhibit inappropriate responses (Swick et al., 2012). The co-occurrence of mTBI with PTSD did not worsen the response inhibition deficit associated with PTSD alone. The severity of self-rated PTSD and depressive symptoms correlated with the degree of behavioral impairment on the task.
- Observed that the patients showed significantly greater trial-to-trial variability in their reaction times in the Go/NoGo task, which suggests a reduction in the stability of executive control processes over time. A paper describing these results is in preparation.
- Determined that the PTSD/mTBI patients showed a slight reduction in the electrophysiological correlate of error processing, the error-related negativity (ERN), although this was not significant. The combination of co-morbid depression, PTSD, and mTBI may have had differential effects on this ERP measure.
- Demonstrated that the PTSD/mTBI patients showed intact performance in a flanker interference task under both single-task and dual-task conditions, suggesting that some types of executive control processes are intact.
- Prepared the draft of a manuscript showing that working memory performance is compromised in PTSD/mTBI patients when additional cognitive demands require multitasking (Honzel et al., in preparation). The patients also showed a reduction in the electrophysiological correlate of working memory retrieval in the dual task condition only.
- Initiated a new set of analyses of EEG activity during the encoding and delay intervals of the Sternberg memory task. Preliminary results are suggestive of spectral differences between the controls and PTSD patients during encoding. Specifically, power in the theta and alpha bands tends to be larger for controls in the dual task condition.
- Demonstrated that PTSD/mTBI patients are as good as or better than controls at suppressing information that is no longer relevant, when the stimuli are neutral and unrelated to combat trauma.

REPORTABLE OUTCOMES:

Publications

Swick, D., Honzel, N., Larsen, J., Ashley, V., & Justus, T. (2012). Impaired response inhibition in veterans with post-traumatic stress disorder and mild traumatic brain injury. *Journal of the International Neuropsychological Society* 18:1-10.

<http://dx.doi.org/10.1017/S1355617712000458>

Ashley, V., Honzel, N., Larsen, J., Justus T., & Swick D (submitted). Attentional bias for trauma-related words: Exaggerated emotional Stroop effect in Afghanistan and Iraq war veterans with PTSD.

Honzel, H., Justus, T. & Swick, D. (draft). Post-traumatic stress disorder is associated with limited executive resources in a working memory task.

Abstracts

Ashley V, Larsen J, Pratt N, Swick D. (2012). Impaired identification of facial expressions of fear in Iraq war veterans with PTSD and mTBI. Poster presented at the Cognitive Neuroscience Society Meeting, March 31 – April 3, 2012.

http://www.cnsmeeting.org/?page=poster_detail&show=authors&sort=board_a&go=&id=902

Presentations

Feb 7, 2012: Data presented at TBI Journal Club, VANCHCS Martinez

Grant Applications

The impact of cognitive deficits in TBI and PTSD on language comprehension. VA Career Development Award submitted to RR&D on 6/6/11, not funded. *Principal Investigator:* Timothy Justus, Ph.D. *Mentor:* Diane Swick, Ph.D.

Electrophysiological markers of concussion symptoms in NFL players. Submitted as Pre-Proposal for NFL Medical Research Grants on 8/17/11, not internally selected by UC Davis. *Principal Investigator:* Diane Swick, Ph.D. *Co-PI:* Nikki Pratt, Ph.D.

The Structure and Function of the Anterior Cingulate Cortex in PTSD. VA Career Development Award submitted to RR&D on 12/6/11, not funded. *Principal Investigator:* Nikki Honzel, Ph.D. *Mentor:* Diane Swick, Ph.D.

Frontal Lobe Injury and Executive Control of Cognition and Emotion. VA Merit renewal submitted to CSR&D on 3/12/12, pending (Percentile: 7.3, recommended for funding). *Principal Investigator:* Diane Swick, Ph.D.

CONCLUSION: Executive control over cognition and emotion is critical for avoiding undesirable behavioral response patterns at home, school and work. These cognitive processes are also essential to facilitate recovery from traumatic events and brain injuries, so veterans can return to their usual social and occupational activities. Separating the negative effects of PTSD and mTBI on executive control functions has been difficult, due the paucity of veterans who have probable mTBI due to blast exposure in the absence of PTSD and other psychiatric symptoms. The majority of veterans recruited at VANCHCS have mTBI+PTSD (71%), with 23% diagnosed with PTSD only, and a mere 6% with mTBI only. Does mTBI increase vulnerability to PTSD due to brain injury, or because both conditions involve exposure to traumatic events in the military theater? Although it is impossible to determine causality from our results, we and others have observed no differences in PCL-M scores in PTSD patients with vs. those without co-morbid mTBI. Furthermore, the severity of mTBI (number, loss of consciousness) did not affect PCL-M scores, either (Swick et al., 2012).

Three areas emerged where the PTSD/mTBI participants showed strengths in executive control functions: overriding conflicting response cues in a flanker task (see Phase 4B), overcoming proactive interference in working memory, i.e., suppressing material that is no longer relevant (Phase 4E), and stopping a motor response that was already planned (Stop Signal Task, reported in Year 3).

These strengths are closely related to other executive functions that were weaker in the PTSD/mTBI participants. They showed pronounced deficits in motor response inhibition (Phase 3B), consistency in responding (Phase 3C), and control over emotional reactions to trauma reminders (Phase 3A). Although they were not uniformly impaired in multitasking (Phase 4B), the patients showed behavioral and electrophysiological deficits in working memory retrieval that became apparent only when they performed a secondary task during the delay interval. Ongoing EEG analyses will determine whether the groups show different patterns of neural activity while encoding and remembering a set of letters across a short delay.

Ultimately, these types of dissociations are informative for theoretical models of executive control function, but more importantly for demonstrating that PTSD/mTBI can spare some important cognitive abilities. These strengths could be exploited in future developments of psychotherapy and cognitive rehabilitation techniques.

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APPENDICES

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Attentional bias for trauma-related words:

Exaggerated emotional Stroop effect in Afghanistan and Iraq war veterans with PTSD

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Abstract

Post-traumatic stress disorder (PTSD) involves a constellation of debilitating symptoms that disrupt cognitive functioning. The emotional Stroop task has been commonly used to examine the impact of PTSD on attentional control, but no published study has used it with Afghanistan and Iraq war veterans (Operation Enduring Freedom/Operation Iraqi Freedom; OEF/OIF). We administered the emotional Stroop, the Beck Depression Inventory (BDI), and the PTSD Checklist (PCL) to 30 PTSD patients, 30 military controls, and 30 civilian controls. Stroop word types included Combat, Matched-neutral, Neutral, Positive and Negative. All groups were slower on Combat words but veterans with PTSD were disproportionately slower than controls. They were also slower and less accurate overall, did not show interference on Negative or Positive words relative to Neutral, and showed a trend for a different pattern of habituation to Combat words than controls. Higher PCL and BDI scores correlated with larger interference effects. The emotional Stroop task may serve as a useful pre- and post task with intervention studies with veterans with PTSD, and other groups.

Keywords: Posttraumatic stress disorder, Veterans, Stroop, Trauma, Interference, Habituation

Numerous studies have examined the cognitive and emotional impact on the estimated 10 to 17% of US service members who have returned from the wars in Iraq and Afghanistan with post-traumatic stress disorder (PTSD) (Sundin, Fear, Iversen, Rona & Wessely, 2011; Tanielian & Jaycox, 2008; Hoge et al., 2004; King et al., 2011). However, no studies that we are aware of have used the emotional Stroop to assess this population, a task commonly used to examine attention biases in anxiety and depressive disorders, including PTSD (Buckley, Blanchard & Neill, 2000; Cisler et al., 2011; Williams, Mathews & MacLeod, 1996), and particularly in war veterans with PTSD (Constans, McCloskey, Vasterling, Brailey & Mathews, 2004; Kaspi, McNally & Amir, 1995; Litz et al., 1996; McNally, English & Lipke 1993; McNally, Kaspi, Riemann & Zeitlin, 1990; Shin et al., 2001; Vrana, Roodman & Beckham, 1995).

The combat theaters of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) in Afghanistan and Iraq involved multiple and extended deployments with shorter rest periods, higher wound survivability rates, and large numbers of traumatic brain injuries (TBI) than previous US wars (Tanielian & Jaycox, 2008). PTSD is a disorder involving long-term alteration of physiological and emotional functioning following exposure to horrific events, and typically involves intrusive cognitive and emotional phenomena such as nightmares, flashbacks, memory deficits and biases in attentional allocation (Schnurr, Hayes, Lunney, McFall & Uddo, 2006). Mechanisms that may underlie the attentional biases in PTSD include regulating, inhibiting or extinguishing a fear response following trauma exposure (Jovanovic & Norrholm, 2011; Pole, 2007; Pole et al., 2009).

The emotional Stroop task, a variant of the classic Stroop task, indexes emotional interference by comparing reaction time (RT) differences to name the font color of an emotional word compared to a neutral word, with instructions to ignore the meaning of the word. Healthy individuals are typically

slower to name the colors of negative-valenced words (Phaf & Kan, 2007), and this effect is often robust in individuals with PTSD when color-naming trauma-related words (Buckley, et al., 2000; Cisler, 2011; Williams, Mathews & MacLeod, 1996; however, see Kimble, Frueh & Marks, 2009). The emotional Stroop task has also been shown to be sensitive to malingering -- Buckley, Galovski, Blanchard & Hickling (2003) covertly enrolled professional actors trained to feign PTSD into a treatment outcome study, and found that the actors were unable to replicate the interference effects displayed by the trauma survivors with PTSD.

The mechanisms of interference in the emotional Stroop task have been debated. While earlier studies concluded that emotional words capture attention (McNally, Kaspi, et al., 1990; McNally, et al., 1993; Mogg, Mathews & Weinman, 1989), later studies have found that emotional words are more difficult to disengage from (El Khoury-Malhame et al., 2011; Pineles, Shipherd, Mostoufi, Abramovitz & Yovel, 2009). Other studies suggest roles for both attentional capture and difficulty in disengagement (Aupperle, Melrose, Stein & Paulus, 2011). Being unable to disengage from irrelevant stimuli can not only impact daily life, i.e., the need to focus on the changing color of a traffic light when approaching a busy intersection, but also attention being held sooner and longer by trauma-related reminders may contribute to maintaining attentional biases.

The intractable nature of the response to trauma reminders in PTSD is often cited as a hallmark of the disorder, involving a unique difficulty for PTSD sufferers to habituate, or adapt to, such reminders. For example, some veterans with PTSD who participated in our study described experiencing overwhelming feelings of anger and fear upon getting caught in traffic jams, because it reminded them of their vulnerability to roadside explosive attacks in Iraq. Despite knowing that roadside bombs would not occur in the US, the debilitating overwhelming emotional response was inevitable. Such an inability to habituate to day-to-day trauma reminders is believed to contribute to

the persistence of PTSD. Studies of habituation in PTSD typically find physiological differences in response to trauma-related stimuli (but less so for general negative stimuli) and reliably indicate an altered profile of persistent hyper-arousal, exaggerated startle responses (Fani et al., 2012; Pole, 2007), larger eye-blink, eye pupil, heart rate and slower skin conductance habituation (Metzger et al., 1999).

While most studies of habituation to trauma-related stimuli in PTSD have measured physiological responses, at least one has used the emotional Stroop (McNally, Amir & Lipke, 1996). Habituation using the emotional Stroop is defined as diminished emotional interference effects (less RT slowing) combined with increased RT slowing for neutral words, or fatigue effects, over time (McNally, Riemann & Kim, 1990; Witthöft, Rist & Bailer, 2008). The emotional Stroop has been used to assess habituation to relevant emotional words with healthy adults (McKenna & Sharma, 1995), individuals with panic disorder (McNally, Riemann & Kim, 1990), individuals with elevated health anxiety (Witthöft, et al., 2008) and veterans with PTSD (McNally, Amir & Lipke, 1996). McNally, Amir & Lipke (1996) compared RTs by Vietnam combat veterans with and without PTSD over 4 mixed blocks of words (96 words each), in response to 4 word types: trauma, positive, neutral and color words. In a block by block comparison, they found that PTSD patients showed trauma-specific interference effects on the first block, and then habituated to the content of the trauma words over time, becoming indistinguishable from controls by the end (McNally, Amir & Lipke, 1996).

PTSD patients often show significant interference to only trauma-related stimuli, rather than general negative or threat-related stimuli (McNally, Kaspi, et al., 1990; McNally, et al., 1993), however, studies do not agree on this finding (Cisler, 2011; Kimble, et al., 2009). For example, Litz et al. (1996) found Stroop interference effects for veterans color-naming high-threat words unrelated to their trauma, suggesting that PTSD patients may display interference effects from all high-threat words, rather than just trauma-related words. Findings that PTSD patients show a specific bias for trauma-

related words, and not generally negative or threatening words, supports the idea that the emotional Stroop may index PTSD, rather than exposure to trauma (with or without PTSD). In order to examine the apparent specificity in PTSD for threat-related words in the current study, rather than using only threat-related and matched neutral words, we used five different word types: Combat, Matched-neutral, Negative, Positive and Neutral. Combat and Matched-neutral were each compared, and then separately, Negative, Positive and Neutral were each compared. This separation kept variables such as word frequency, valence, arousal, and other properties as consistent as possible across comparisons.

Having a military control group (MC) that experienced the same trauma environment as PTs was important to distinguish between trauma exposed individuals with and without PTSD (13 out of 30 MCs were deployed to Iraq or Afghanistan during the OEF/OIF wars). Additionally, to reveal any possible Stroop effects due to military work conditions and lifestyles, we also included a healthy civilian control group (CC).

Additionally, many emotional Stroop studies of PTSD have included small numbers of words and have repeated them. However, when words are repeated, a potential confound is introduced between whether any observed habituation is due to perceiving the same word more than once, or to adapting to the semantic content of the word, or both. Consequently, we used all unique words in the current study.

The primary goal of our study was to expand on the dominant findings of the majority of emotional Stroop studies with PTSD patients, in which, compared to controls, PTSD patients exhibit significant interference (RT slowing) and increased errors on trauma-related words. First, given the specificity of the deficit in PTSD to trauma-related stimuli, we predicted that veterans with PTSD would show less interference from Negative words relative to Neutral, then from Combat words relative to Matched-neutral. Next, in keeping with one previous study examining habituation to trauma

words with an emotional Stroop (McNally, Amir & Lipke, 1996), we also expected veterans with PTSD to show diminished habituation to Combat words. Finally, we predicted that Stroop interference would correlate positively with scores on the PTSD checklist (PCL) and the Beck Depression Inventory (BDI) for all subjects.

METHODS

Participants

Thirty OEF/OIF war veterans with PTSD (29 males) (PTs), thirty age-matched military controls (28 males) (MCs), and thirty age-matched civilian controls (30 males) (CCs), participated in the study. Demographic information is shown in Table 1. PTSD diagnosis was based on a clinical interview using DSM-IV criteria. Mild TBI was diagnosed based on a clinical interview and patient self-report of the following criteria from the VA/DoD Clinical Practice Guidelines – loss of consciousness 30 min or less or altered mental status (e.g., feeling dazed, disoriented, or confused), with post-traumatic amnesia less than 24 hrs (The Management of Concussion/mTBI Working Group, 2009). Twenty-two of the 30 PTSD patients reported or were diagnosed with a mild traumatic brain injury (TBI), typically due to IED blast exposure. Diagnoses of mTBI and PTSD were corroborated with available VA medical records to the fullest extent possible.

Participants were recruited from clinics at the Veterans Affairs of Northern California Health Care System, fliers placed in local military offices, and internet postings. Subjects signed informed consent forms approved by the Institutional Review Board of the Veterans Affairs Medical Center and were paid \$20/hr plus travel after completion of the session. Control groups were matched for age and gender but not education ($p < .0003$). Previous emotional Stroop studies of veterans with PTSD have also noted difficulty in matching groups of veterans on years of education (e.g., McNally, Kaspi, et al.,

1990; Vrana, et al., 1995). Exclusion criteria included any neurological or additional psychiatric disorders (i.e., schizophrenia, bipolar, epilepsy), or having PTSD not due to OEF/OIF events (i.e., due to the Vietnam war, car accident, etc.). Six participants who were initially enrolled were subsequently removed from the study (4 patients, 2 controls), when it was found they met exclusionary criteria (childhood TBI; nonmilitary PTSD; moderate TBI; other psychiatric disorder; not OEF/OIF). Two other participants did not complete the emotional Stroop task and were also subsequently removed from the study (2 patients). All subjects reported English as their first language.

Materials

Following the emotional Stroop task, subjects were asked to complete the 17-item PTSD Checklist, Military or Civilian Version (PCL-M or PCL-C) (Weathers, Litz, Huska & Keane, 1994) to assess their level of PTSD symptoms during the past month. The PCL is a widely used 17-item self-report measure of the DSM-IV symptoms of PTSD (Weathers, Litz, Herman, Huska & Keane 1993). Patients and military controls received the PCL-M (military), which asks about symptoms they have been bothered by in the past month due to "stressful military experiences". The PCL-C (civilian) was given to civilian controls and asks about symptoms in response to "stressful experiences". All subjects were also given the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), to assess levels of depression in the past few days. The BDI is a commonly used 21-item self-report screen for major depressive disorder (MDD) that has been validated with well-established psychometric properties (Ambrosini, Metz, Bianchi, Rabinovich & Undie, 1990; Beck, Steer & Gabin, 1988).

Stimuli were colored words (red, blue, green, or yellow) shown one at a time in the center of a computer screen in 48 pt Times font, using all capital letters, on a black background at a distance of approximately 30 cm from the viewer. Colors did not repeat on consecutive words and were equally

used throughout all trials. The task included 5 blocks of words, with each block containing a single word category. The five categories of words were: 1) “Combat”: trauma-related words based in events of the OEF/OIF wars in Iraq and Afghanistan (i.e., *detainee, warlord, Falluja*); 2) “Matched-neutral”: words matched to combat words in number of letters and frequency (i.e., *detective, faculty, Jakarta*); 3) “Positive” (i.e., *proud, comedy, diamond*); “Negative” (i.e., *fraud, stupid, tragedy*) and “Neutral” (*sleep, poster, mixture*).

Combat and Matched-neutral words: We created the Combat word list from a search of mainstream media news stories, soldier blog entries, and other public sources describing unique and traumatic aspects of the OEF/OIF war experience. Typical OEF/OIF combat stressors included exposure to improvised explosive device (IED) blasts and suicide bombers, seeing human remains, engaging in killing another person, experiencing violent deaths and injuries of fellow soldiers and friends, and being unable to stop violent situations (Hoge et al., 2004). Four types of Combat words were used: 1) Words associated with the OEF/OIF combat events (i.e., *insurgent*), 2) Place names (i.e., *Kirkuk*), 3) Military abbreviations (i.e., *IED*), and 4) General war trauma words (i.e., *gunmen*). Matched-neutral words were created by finding words neutral in valence to match Combat words on number of letters, syllables, word type and frequency (see Appendix A).

Neutral, Negative and Positive words: Neutral, Negative and Positive words were matched on number of letters, number of syllables and frequency. Only high arousal Negative and Positive words were used and arousal and valence ratings for Neutral, Negative and Positive words were based on the Affective Norms for English Words (ANEW, Bradley & Lang, 1999). ANOVAs were conducted to examine any word type differences. Mean valence ratings were as follows: Positive: 7.6 (SD=0.5, range=7.0–8.7), Negative: 2.6 (SD=0.6, range=1.3-3.9) and Neutral: 5.3 (SD=1.1, range=1.9-7.9).

Arousal levels for both Positive (mean=5.8, SD=0.6) and Negative words (mean=5.8, SD=0.9) were higher than Neutral (mean=3.6, SD=0.4) ($p<.0001$). No significant differences between word categories were found using the Hyperspace Analogue to Language (HAL) frequency norms ($p=0.69$) from the online database of the English Lexicon Project (ELP) (<http://ellexicon.wustl.edu>) (Balota et al., 2007).

Procedure

All participants were instructed to name the color of a word shown on the computer screen by speaking into a voice-activated microphone as quickly and as accurately as possible. Participants started with 15 neutral word practice trials. Words were presented for 500 ms using Presentation software (Neurobehavioral Systems Inc., CA, USA), with a total trial time of 2000 ms and an inter-stimulus interval of 1500 ms. Each of the 5 blocks contained 84 words for a total of 420 unique words. Each block took approximately 3 minutes to complete and the study lasted between 15 and 20 minutes. Within blocks, words were presented in fixed pseudo-randomized order.

Because emotional stimuli can contaminate later non-emotional stimuli with carry-over slowing effects, the order of presentation of trials and blocks in an emotional Stroop study should attempt to counterbalance such effects (Lundh & Czyzykow-Czarnocka, 2001; Witthöft, et al., 2008). We used a Latin Square design employed by McKenna and Sharma (1995, 2004) to counterbalance order effects of different word types in a blocked design format across all participants. Blocks were counterbalanced using a balanced 5 x 5 Latin Square design (Newcombe, 1992; Wagenaar, 1969) in which subjects received one of 10 possible block orders (5 block orders mirrored the other 5). Each of the 10 different Latin Square orders was repeated 3 times within each group ($n=30$). The PCL and BDI questionnaires were administered on paper after the Stroop task.

RESULTS

Only correct responses were included in results analyses (average percentage of error RTs removed: PTSD PTs=3.53%; Military Controls=1.56%; Civilian Controls=1.61%). Behavioral exclusion criteria included participants with more than 25% error rates (Wurm, Labouvie-Vief, Aycock, Rebucal & Koch, 2004) and no participants met that level. Trial reaction time data were trimmed to decrease variance such that RTs longer than 2 SDs above the subject's block mean (Kingma, La Heij, Fasotti & Eling, 1996; Verbruggen, Liefvooghe & Vandierendonck, 2004), and RTs beyond 3000 ms or faster than 200 ms (i.e., artifacts such as coughs or other sounds) (Ashley & Swick, 2009), were removed.

Reaction time and accuracy were each examined with a 3 x 5 Mixed Repeated Measures ANOVA, with Group (PTs, MCs, CCs) as the between-subjects factor and Word Valence (Combat, Matched-neutral, Neutral, Negative, Positive) as the within-subjects factor. When contrasts were not planned, a correction for multiple comparisons of $p < .005$ was used.

Reaction times

Color-naming

Reaction time results indicated a significant main effect of Group, $F(2,87)=7.75$, $p=.0008$, with overall RTs for PTs slower than either Control group (Means: PTs=726 ms, MCs=604 ms, CCs=599 ms). A significant main effect was also shown for Valence, $F(4,8)=26.16$, $p<.0001$, with all groups slower on Combat words relative to Matched-neutral words ($p<.02$), confirming the emotional Stroop effect (see Fig 1). An interaction effect for Valence x Group, $F(8,348)=3.87$, $p=.0002$, indicated that group RTs differed depending on word type, with PTs showing greater slowing for Combat versus Matched-neutral than controls.

Combat and Matched-neutral: Within group planned paired t-test comparisons of Combat and Matched-neutral blocks showed that each group was slower on Combat words: PTs: $t(1,29)=6.47$, $p<.0001$; MCs $t(1,29)=2.81$, $p=.009$; and CCs $t(1,29)=2.63$, $p=.01$. A between-groups ANOVA analysis of RTs to Combat and Matched-neutral blocks showed a robust interaction of Valence x Group, $F(2,87)=8.53$, $p=.0004$, indicating that although all groups were slower on Combat words, PTs had greater slowing than either control group.

Neutral, Positive and Negative: Between group ANOVAs examining mean RTs on Negative versus Neutral and Positive versus Neutral blocks showed main effects of Group [Negative: $F(2,87)=7.18$, $p=.001$; Positive: $F(2,87)=6.76$, $p=.002$], with PTs significantly slower overall, but no significant group interactions (Negative: $p=.11$; Positive: $p=.08$). Within group planned paired t-test comparisons indicated that MCs were slower on Negative versus Neutral, $t(1,29)=3.67$, $p=.001$, and had a non-significant trend for being slower on Positive versus Neutral, $t(1,29)=1.81$, $p=.08$. CCs showed no significant differences on Negative versus Neutral, ($p=.61$), or Positive versus Neutral ($p=.405$). PTs were significantly slower on Negative versus Positive, $t(1,29)=1.79$, $p=.009$, and MCs displayed a trend for the same finding, $t(1,29)=1.79$, $p=.083$ (see Table 2).

Thus, PTs did show a large interference effect on Combat words (112 ms; $p<.0001$) but not on Negative relative to Neutral (19 ms; $p=.18$). In contrast, MCs showed interference effects of a similar size on both Combat (41 ms; $p=.009$) and Negative (41 ms; $p=.001$) and CCs showed an interference effect by Combat words similar to MCs (33 ms; $p=.01$) but no other significant effects.

To test whether the lower education in the PT group affected the findings of the study, we examined a subset of both control groups with lower education ($n=32$) to match with the PT group [mean education in years: PTs: 13.12; MCs: 13.44; CCs: 13.3 ($p>.41$)] and found that overall group RTs were still significantly different, $F(2,59)=4.83$, $p=.01$, and that the Group x Valence interaction still

existed, $F(8,236)=2.26$, $p=.02$. The results were the same for the error analysis: while overall group accuracy was still significantly different, $F(2,59)=6.12$, $p=.004$, the Group x Valence interaction did not reach significance, $F(8,236)=.886$, $p=.53$. Only 7 MCs reported active combat, whereas all of the veterans with PTSD reported active combat. A between-groups ANOVA (MCs Deployed versus MCs Not Deployed) analysis of RTs did not find any overall group differences ($p=.29$) or Group x Valence interaction ($p=.11$). However, because the Latin Square order is not balanced in this type of analysis, the validity of such comparisons is difficult to determine.

Habituation

We analyzed habituation effects across the length of the Combat and Matched-neutral blocks (84 trials each) by comparing average RTs during each quarter of the blocks: “First quarter” (trials 1-21), “Second quarter” (trials 22-42), “Third quarter” (trials 43-63) and “Fourth quarter” (trials 64-84). The choice of quarters was based on the number of trials in the habituation analysis by Witthöft, et al. (2008), which compared groups during the first and second halves of blocks (trials 1-20 and 21-40), and the emotional Stroop studies by McNally, Riemann & Kim (1990) and McNally, Amir & Lipke (1996), which analyzed 4 different word types, each occurring on 20 and 24 trials per mixed block (with each block being 100 and 96 trials in length), respectively.

We analyzed RTs in a repeated measures 3 (Group) x 4 (Quarter) x 2 (Valence) ANOVA. Results showed an interaction effect of Valence x Group ($p=.0008$), no interaction of Quarter x Group ($p=.54$), and a trend for the 3-way interaction of Quarter x Valence x Group ($p=.09$) (See Fig 2a). Planned t-test comparisons confirmed that PTs were slower on Combat words on all quarters, Q1: $t(1,29)=5.1$, $p<.0001$; Q2: $t(1,29)=5.0$, $p<.0001$; Q3: $t(1,29)=5.1$, $p<.0001$; Q4: $t(1,29)=2.9$, $p=.007$, while both control groups were slower only on quarter 1 (MCs: $t(1,29)=2.8$, $p=.01$; CCs: $t(1,29)=2.7$, $p=.01$), with intermittent slowing on other quarters (MCs: Q4, $p=.02$; CCs: Q3, $p=.005$).

In an analysis similar to McNally, Amir & Lipke (1996), who found that trauma-related interference for veterans with PTSD was apparent only on the first of four blocks in a block by block analysis, we analyzed each quarter using a 2 (Group) x 2 (Valence) repeated measures ANOVA. Results indicated a significant Valence x Group interaction on quarters 1 – 3 (Q1: $F(2,87)=6.48$, $p=.002$; Q2: $F(2,87)=6.7$, $p=.002$; Q3: $F(2,87)=7.24$, $p=.001$), but not on quarter 4 (Q4: $F(2,87)=1.81$, $p=.17$). PTs showed a strong interference effect (over 120 ms) from Combat words during the first 3 quarters of the block, which decreased to 64 ms in the last quarter (See Fig 2a), while control groups never showed more than 41 ms of interference slowing (See Table 3). These results suggest that although veterans with PTSD displayed a tendency for exaggerated interference effects from trauma-related stimuli across the full length of the block, by the last quarter, the groups were no longer different. Thus, PTs tended to differ from Controls for up to 63 trials, but appeared to habituate in the last quarter of the block.

Accuracy

An ANOVA conducted for accuracy scores showed a significant main effect of Group $F(2,87)=9.99$, $p=.0001$, indicating that PTs were less accurate than Control groups overall (average percent accuracy: PTs: 96.6; MCs: 98.4; CCs: 98.5). A main effect of Valence was also shown, $F(4,8)=4.87$, $p=.0008$, in which PTs were less accurate than Controls on all word types ($p<.04$) except Neutral ($p>.07$). A trend for a Group x Valence interaction was indicated ($p=.11$). Planned t-test comparisons of accuracy on Combat words showed that PTs were less accurate on Combat words relative to Control Groups, $t(1,58)=-3.1$, $p<.003$.

A speed-accuracy trade-off analysis using Spearman correlations indicated that CCs exchanged accuracy for speed on the Combat and Matched-neutral blocks: $r(1,28)=.425$, $p=.02$, while the trade-offs for PTs and MCs did not reach significance ($p<.12$). No other word types showed any significant

speed-accuracy trade-off outcomes.

Combat and Neutral Combat: Planned paired t-test comparisons of Combat and Matched-neutral words within each group indicated a trend for PTs to be less accurate on Combat words, $t(1,29)=1.97, p=.06$, and no differences for Control groups, (MCs: $p=.54$; CCs: $p=.77$).

Neutral, Positive and Negative: Planned paired t-test comparisons within each group for Neutral, Positive and Negative words revealed no accuracy differences ($p>.14$).

Self-Report questionnaires

PTSD patients reported higher PCL scores (58.1) than the military (27.1) or civilian (26.0) control groups, $F(2,87)=51.2, p<.0001$ (PTs vs MCs:) and higher BDI scores (20.4) than the military (6.3) or civilian (3.0) control groups, $F(2,87)= 85.1, p<.0001$. Bonferroni comparisons between control groups indicated a non-significant trend for differences in depression on the BDI and no significant differences on the PCL (BDI, $p=.07$; PCL, $p=.70$).

Correlations between experimental and self-report measures

Spearman correlations conducted between the PCL and BDI self-report measures and behavioral performance indicated interference from Combat words (larger RT difference for Combat minus Matched-neutral blocks) correlated positively with increased depression scores on the BDI ($\rho=.36; p=.0007$), and PTSD symptoms on the PCL ($\rho=.33; p=.002$). Within the PCL, the PTSD symptom clusters of re-experiencing ($\rho=.38; p=.0005$), hyper-arousal ($\rho=.33; p=.002$), and avoidance/numbing ($\rho=.25; p=.02$) also showed significant positive correlations.

DISCUSSION

We found that OEF/OIF veterans with PTSD had significantly more interference on trauma-related words relative to controls and displayed slower RTs and lower overall accuracy, replicating the

findings of several previous studies using the emotional Stroop task with veterans with PTSD (Constans, et al., 2004; Kaspi, et al., 1995; Litz et al., 1996; McNally, et al., 1993; McNally, Kaspi, et al., 1990; Shin et al., 2001; Vrana, et al., 1995). Veterans with PTSD did not show interference on Negative or Positive words relative to Neutral, suggesting that their emotional Stroop response was specific to Combat words, but they also tended to display habituation to these same Combat words, despite each word being novel and relatively specific to the OEF/OIF trauma environment. Additionally, across groups, responses on the PCL and BDI questionnaires were positively correlated with percent interference slowing on Combat words, suggesting that increased severity of PTSD and depression symptoms were related to increased difficulty in inhibiting emotional interference on the task.

Our study differed from most previous emotional Stroop studies of PTSD in that all groups -- rather than only veterans with PTSD -- showed significant interference from Combat words. This outcome may be due to the use of particularly salient and intense trauma-related words (i.e., *decapitate*, *abduct*, *severed*, *torture*) and that none of the words repeated. Many studies of PTSD using the emotional Stroop use fewer and less unique words (i.e., *medevac*, *firefight*) and / or use words which are repeated (McNally, et al., 1996; McNally, et al., 1993; Vrana, et al., 1995; Witthöft, et al., 2008). This design was used to assist in finding habituation effects, which could be diminished or confounded if words were repeated. It also delineated larger interference effects, as indicated by the fact that all groups showed interference effects to Combat words, and that despite this, PTs still had a significantly larger interference effect relative to Controls.

Our study also examined habituation effects (RT decrease to Combat words) to assess the impact of trauma-related stimuli on veterans with PTSD over time. Hyperarousal and hypervigilance are characteristics of PTSD which may contribute to deficits in habituation, resulting in difficulty

adapting to repeated exposure to trauma-related stimuli. We found that veterans with PTSD exhibited consistently strong interference to Combat words (over 100 ms) for up to 63 trials. The only other study to use the emotional Stroop to examine habituation to trauma-related stimuli for veterans with and without PTSD over time (McNally, Amir & Lipke, 1996), found group differences, but only in the first of 4 blocks, and only as a linear pattern of RT decreases over time. However, that study included just 12 different trauma-related words repeated 8 times using a mixed, rather than pure, block design. It is likely that methodological differences, as well as the novel, intense and trauma-specific nature of our word stimuli, led to the persistent substantial interference effects seen in the current study. Importantly, however, despite the initial impact of the words, veterans with PTSD did tend to habituate and reach a color-naming response rate statistically indistinguishable from Controls by the last quarter of the Combat block.

Veterans with PTSD also showed significantly slower response times overall, relative to Controls. This finding is supported by other studies using the emotional Stroop to assess PTSD, which have found that generally, PTSD participants respond slower relative to healthy controls (Fleurkens, Rinck & van Minnen, 2011, Shin et al., 2001; Vrana, et al., 1995). However, a recent study using a classic Stroop with OEF/OIF veterans with co-morbid PTSD and TBI (Nelson, Yoash-Gantz, Pickett & Campbell, 2009) also found overall slowing in PTSD patients. And interestingly, the results on a GoNoGo task administered to all subjects in this study indicated a striking lack of mean RT differences between PTs and Controls, although the PTSD patients had significantly more variability and errors (Swick, Honzel, Larsen, Ashley & Justus, 2012). Whether the overall slowing in our study could be due to the involvement of trauma-related emotional content, or some other factor, cannot be determined and remains to be examined in future research.

The question of whether emotional Stroop interference from trauma-related words reflects

specific characteristics of PTSD, or only the consequences of exposure to traumatic events, has been debated in the literature. Kimble et al. (2009) has argued that RT differences seen in an emotional Stroop may be due to a self-relevant event, the trauma, and not to PTSD. And a recent study on visual attention to threatening stimuli, by Kimble et al. (2011), using eye-tracking, found that Iraq veterans with PTSD were biased towards all negatively valenced stimuli, rather than just Iraq-specific stimuli. Similarly, a meta-analysis by Cisler et al. (2011) suggests that the emotional Stroop task indexes exposure to trauma, rather than PTSD itself. However, several other studies have found results supporting the idea that the emotional Stroop can index PTSD specifically (Fleurkens, et al., 2011; Mueller-Pfeiffer et al., 2010; Pineles, Shipherd, Welch & Yovel, 2007; Pineles, et al., 2009).

In our study, the impact of trauma-related material on PTs appeared to eclipse the effects of Negative words, with Combat words generating much larger interference effects than Negative words. Veterans with PTSD sometimes reported feeling as though they were “awoken” by exposure to the Combat words, relative to the other blocks, and were perplexed by the experience in which they “could not take their eyes off the words”. Importantly, PTs showed no difference on Negative relative to Neutral words, an effect opposite to standard emotional Stroop results using a blocked design (McKenna & Sharma, 2004; Phaf & Khan, 2007). In contrast, MCs displayed the same slowing on Negative relative to Neutral as they did to Combat-related relative to Matched-neutral words (41 ms each). That the elevated emotional Stroop effect in PTs was specific to Combat words and did not generalize to other negative words, is supported by other studies that have found that the emotional Stroop task can index PTSD specifically (Fleurkens, et al., 2011; Mueller-Pfeiffer et al., 2010; Pineles, et al., 2007; Pineles, et al., 2009). Other factors related to PTSD may also be involved in these results, such as numbing. For example a recent study of perceptual processing advantages for trauma-related information (but not for general threat pictures) in patients with PTSD and Acute Stress Disorder

suggested that reduced awareness of stimuli considered safe and normal may play a role in the development and persistence of PTSD (Kleim, Ehring & Ehlers, 2012).

It should be noted that any study investigating groups of war veterans may be limited by the availability of a completely comparable control group – that is, healthy veterans deployed to the war zone, engaged in active combat and exposed to trauma, but without PTSD or TBI and available and motivated to participate in research. Within our group of 30 MCs, 13 were deployed to Iraq or Afghanistan and exposed to the OEF/OIF combat environment, without PTSD or TBI. In the case of the OEF/OIF wars, studies suggest that the factor of deployment alone (without combat or injury), compared with non-deployment, has been associated with neuropsychological compromise on basic cognitive tasks (Vasterling et al., 2006). However, in our study there were no differences between MCs who were deployed (and potentially exposed to traumatic events) and those who were not.

The importance of diagnosing and treating PTSD cannot be understated. As a disorder involving high levels of stress, PTSD is associated with alterations in the hypo-thalamic pituitary-adrenal (HPA) axis and cortisol levels (Yehuda, 2002), increased coronary atherosclerosis and myocardial infarction (Ahmadi et al., 2011), and a nearly 2-fold-higher risk of developing dementia (Yaffe et al., 2010). Rapaport, Clary, Fayyad & Endicott (2005) found that 59% of patients with PTSD have severe impairments in quality of life, and Sher and Yehuda (2011) cite a "suicide epidemic" among OEF/OIF veterans due to the extreme stress of deployment. Treatments for veterans with PTSD in particular must also address not only the characteristic hyperarousal, hypervigilance and numbing symptoms, but also the various physiological alterations from deployment and prolonged stress, for example, chronic sleep restriction and reversed circadian cycles (Hoge, 2011). The results of the current study indicate that, despite these many challenges, veterans with PTSD do appear to habituate to trauma-related stimuli over time, a finding in line with broad support for exposure therapy treatments

for PTSD.

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Ashley - Attentional bias for trauma-related words

Figure Legends

Figure 1a – Reaction times for all blocks of word types. Error bars depict standard errors.

Figure 1b – Mean Stroop interference scores (Combat RTs minus Matched-neutral RTs). Error bars depict standard errors.

Figure 2a – Mean reaction times for Combat (solid lines) and Matched-neutral (dashed lines) blocks across quarters. Error bars depict standard errors.

Figure 2b – Mean Stroop interference scores across quarters (Combat RTs minus Matched-neutral RTs). Error bars depict standard errors.

Table 1

Demographic Information and Self-Rating Scores for Patient and Control Groups

	Patients (n=30)	Military Controls (n=30)	Civilian Controls (n=30)
Age (yrs)	32.3 \pm 7.9 (ns) (24-51)	33.6 \pm 8.3 (23-48)	32.2 \pm 8.3 (20-49)
Education (yrs)	13.1 \pm 1.5 (***) (8-16)	14.6 \pm 1.7 (12-18)	14.8 \pm 1.8 (12-20)
Handedness	27 R, 2 L, 1 ambi	26 R, 4 L	29 R, 1 ambi
Deployed (n)	30	19	---
Combat (n)	26	8	---
BDI	19.9 \pm 9.3 (***)	5.5 \pm 7.0	3.0 \pm 3.16
PCL	57.7 \pm 11.9 (***)	26.5 \pm 10.9	26.0 \pm 9.72

Note. The mean \pm standard deviation and range are given for age and education. n.s. = not significantly different from control groups; *** significantly different from control groups at $p < .001$; R = right, L = left, ambi = ambidextrous; LOC = loss of consciousness (of 30 patients with mTBI, 21 had LOC, 5 did not, and 4 were not sure whether they had LOC); PCL = PTSD checklist; BDI = Beck Depression Inventory.

Table 2

Summary of Word Type Comparisons by Group

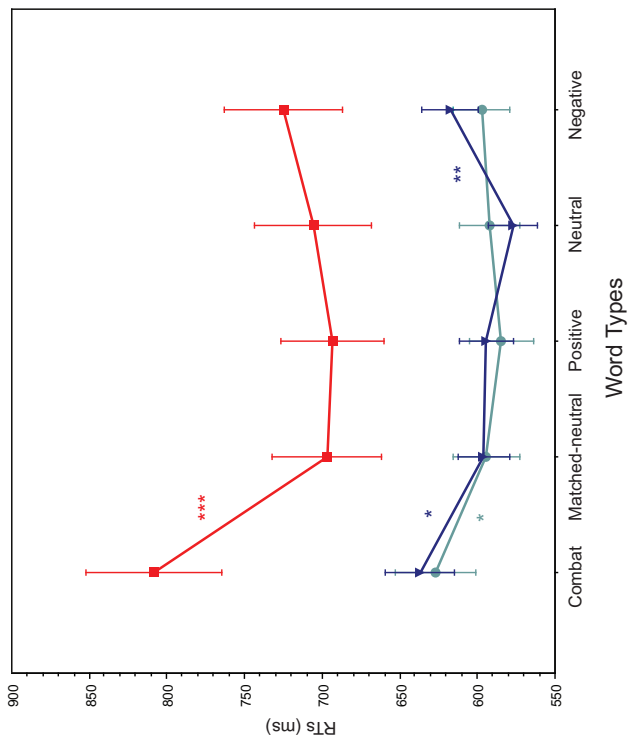
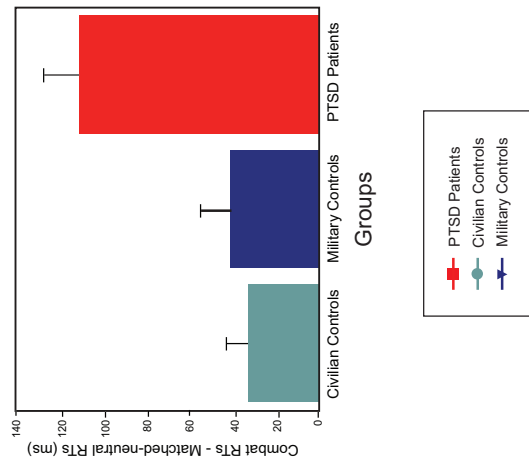
Group	Comparison	RT difference	<i>p</i>
PTSD Patients	Combat vs Matched-neutral	112 ms	$p<.0001$
	Negative vs Neutral	19 ms	$p=.19$
	Positive vs Neutral	13 ms	$p=.26$
Military controls	Combat vs Matched-neutral	41 ms	$p=.009$
	Negative vs Neutral	41 ms	$p=.001$
	Positive vs Neutral	18 ms	$p=.08$
Civilian Controls	Combat vs Matched-neutral	33 ms	$p=.01$
	Negative vs Neutral	5 ms	$p=.61$
	Positive vs Neutral	7 ms	$p=.41$

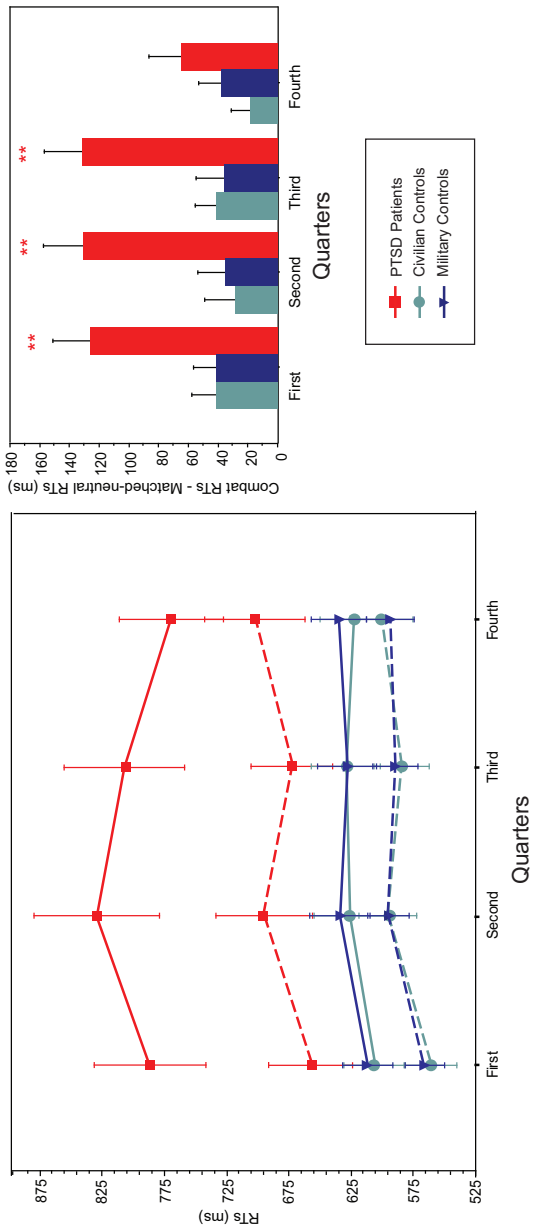
Table 3

Stroop Interference Across Block Quarters

	Patients	Military Controls	Civilian Controls
First Quarter	126.35 ms	41.66 ms	41.82 ms
Second Quarter	131.23 ms	35.18 ms	27.99 ms
Third Quarter	131.35 ms	35.89 ms	41.62 ms
Fourth Quarter	64.36 ms	38.02 ms	18.73 ms

Note: Interference reaction times (RT) reflect Combat RT minus Matched-neutral RT.





APPENDIX

Word lists for each category. Combat and matched neutral words include general combat words, city names, words unique to OEF/OIF, and abbreviations.

<i>Positive</i>	<i>Negative</i>	<i>Neutral</i>	<i>Combat</i>	<i>Matched-Neutral</i>
hug	cut	boy	gun	van
joy	mad	hay	war	net
car	hit	shy	body	city
dog	lie	cat	bomb	week
eat	sin	bus	kill	move
sun	rat	air	tour	ride
toy	fat	bed	vest	vine
gift	hurt	door	medic	tenor
fame	dump	milk	shell	quote
cute	foul	dirt	abduct	obsess
grin	mold	slow	ambush	gossip
idea	rude	silk	Apache	Athena
snow	pity	seat	captor	caddie
song	jail	foot	combat	bottle
star	sick	safe	convoy	pastry
heal	lost	lamp	gunmen	sitter
baby	tomb	item	gunner	jurors
cake	burn	farm	kidnap	peruse
cozy	debt	bowl	martyr	dining
jolly	trash	bench	mortar	comets
proud	crime	rusty	patrol	skiing
puppy	slime	habit	sniper	tenant
honor	crude	bland	terror	permit
humor	slave	salad	weapon	expert
brave	roach	metal	airlift	roofing
lucky	alone	quart	captive	sunrise
music	scorn	plant	execute	examine
merry	loser	horse	explode	consume
loyal	blind	jelly	gunfire	biscuit
treat	snake	wagon	hostage	seniors
learn	dirty	slush	infidel	puritan
loved	filth	table	militia	antenna
silly	stink	sleep	missile	founder
truth	drown	chair	severed	resumed
child	thief	bored	suicide	faculty
cheer	fever	board	torture	thunder
glory	fraud	elbow	trigger	housing
champ	flood	tower	warfare	booklet
palace	malice	pencil	wounded	rounded
dollar	broken	solemn	amputate	renovate

dancer	wicked	poster	casualty	tapestry
strong	misery	violin	evacuate	unifying
travel	offend	square	militant	partisan
comedy	rotten	window	prisoner	observer
dinner	stupid	sphere	roadside	newsroom
savior	horror	gentle	shrapnel	trustees
mother	crisis	golfer	blindfold	blueprint
riches	hatred	moment	crossfire	staircase
bright	damage	butter	explosive	undefined
talent	rabies	engine	insurgent	condiment
joyful	poison	finger	checkpoint	paintbrush
trophy	insane	museum	concussion	complexion
honest	insult	basket	decapitate	redecorate
scholar	selfish	obesity	projectile	dishwasher
admired	tragedy	comfort	Anbar	Cairo
sunrise	trouble	packets	Basra	Paris
festive	useless	cottage	Kabul	Delhi
holiday	tornado	cabinet	Mosul	Milan
hopeful	garbage	staples	Bagram	Lisbon
fantasy	lawsuit	staying	Kirkuk	Moscow
devoted	delayed	symbols	Baghdad	Bristol
diamond	illness	cabbage	Falluja	Jakarta
victory	corrupt	shorter	Haditha	Nairobi
justice	outrage	retired	Kandahar	Damascus
liberty	destroy	arrange	caves	trunk
magical	divorce	history	behead	bestow
blossom	penalty	mixture	Mullah	Bishop
improve	poverty	relaxed	Muqtada	Juanita
adorable	disaster	bathroom	Taliban	Chianti
terrific	bankrupt	building	warlord	shipman
vacation	arrogant	umbrella	Zarqawi	Audubon
treasure	troubled	thorough	detainee	detective
inspired	contempt	windmill	firefight	fieldwork
laughter	confused	feathers	Kalashnikov	
luscious	terrible	periodic	HV	UV
exercise	pressure	reserved	RPG	DVD
friendly	jealousy	performs	IED	DNA
champion	rejected	pamphlet	WMD	NBA
sapphire	ridicule	neighbor	APC	NFL
applause	sickness	corridor	CHU	PDA
ambition	starving	spinning	MOUT	RSVP
outdoors	dreadful	curtains	AK-47	BLVD
pleasure	insecure	segments	KMTC	USPS
prestige	helpless	cylinder	VBIED	SCUBA

Impaired Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Mild Traumatic Brain Injury

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Abstract

Combat veterans with post-traumatic stress disorder (PTSD) can show impairments in executive control and increases in impulsivity. The current study examined the effects of PTSD on motor response inhibition, a key cognitive control function. A Go/NoGo task was administered to veterans with a diagnosis of PTSD based on semi-structured clinical interview using DSM-IV criteria ($n = 40$) and age-matched control veterans ($n = 33$). Participants also completed questionnaires to assess self-reported levels of PTSD and depressive symptoms. Performance measures from the patients (error rates and reaction times) were compared to those from controls. PTSD patients showed a significant deficit in response inhibition, committing more errors on NoGo trials than controls. Higher levels of PTSD and depressive symptoms were associated with higher error rates. Of the three symptom clusters, re-experiencing was the strongest predictor of performance. Because the co-morbidity of mild traumatic brain injury (mTBI) and PTSD was high in this population, secondary analyses compared veterans with PTSD+mTBI ($n = 30$) to veterans with PTSD only ($n = 10$). Although preliminary, results indicated the two patient groups did not differ on any measure ($p > .88$). Since cognitive impairments could hinder the effectiveness of standard PTSD therapies, incorporating treatments that strengthen executive functions might be considered in the future. (*JINS*, 2012, *18*, 1–10)

Keywords: PTSD, TBI, Go/NoGo, Executive control, Inhibitory control, Impulsivity

INTRODUCTION

Post-traumatic stress disorder (PTSD) and traumatic brain injuries (TBI) can have detrimental effects on the cognitive and emotional functioning of U.S. veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Impairments in executive control functions are frequently observed in this population (Vasterling, Verfaellie, & Sullivan, 2009). Although the effects of PTSD on executive functions have not received as much attention as the well-documented changes in memory and fear learning, many studies have found that impairments do occur (Koso & Hansen, 2006; Leskin & White, 2007; Vasterling, Brailey, Constans, & Sutker, 1998). Recent reviews have suggested that deficits in attention and executive control can be evident even when the experimental stimuli are emotionally neutral, as opposed to trauma-related

(Vasterling & Verfaellie, 2009; Vasterling et al., 2009; Qureshi et al., 2011). Subtle impairments in executive function could hinder the effectiveness of PTSD treatments that rely on the retrieval of autobiographical memories and cognitive reappraisal techniques, such as prolonged exposure and cognitive processing therapy (Vasterling & Verfaellie, 2009). Furthermore, executive control over thought and behavior is necessary for effective disengagement from an overwhelming preoccupation with traumatic stimuli (Aupperle, Melrose, Stein, & Paulus, 2012).

The lateral prefrontal cortex (PFC) is thought to implement cognitive control by exerting top-down influences over sensory and motor processing (Miller & Cohen, 2001). In addition, the anterior cingulate cortex (ACC) has been implicated in a variety of cognitive tasks that require executive control processes (Botvinick, Cohen, & Carter, 2004; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Swick & Turken, 2002). Response inhibition, or the ability to inhibit prepotent responses, is thought to rely on the integrity of specific regions in the lateral and medial PFC

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(Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Picton et al., 2007; Swick, Ashley, & Turken, 2008). It is a core executive control function that has been dissociated from other higher cognitive processes such as task switching and working memory updating (McNab et al., 2008; Miyake et al., 2000; Nee, Wager, & Jonides, 2007). In PTSD, functional alterations have been observed in the ACC and other medial frontal regions (Etkin & Wager, 2007; Shin, Rauch, & Pitman, 2006), as well as in lateral PFC (Morey, Petty, Cooper, Labar, & McCarthy, 2008). These alterations could account for some of the observed deficits in emotion regulation and inhibitory control functions.

The Go/NoGo (GNG) task has been used extensively to assess response inhibition in both animals (Petrides, 1986) and humans (Swick, Ashley, & Turken, 2011). In this task, a motor response is given to one stimulus class and withheld to another. The NoGo stimuli are typically infrequent to establish a prepotent tendency to respond. Impairments in the GNG task have been observed in clinical populations with inhibitory deficits, such as attention deficit hyperactivity disorder (ADHD), substance abuse, schizophrenia, and borderline personality disorder (Chambers, Garavan, & Bellgrove, 2009; Donohoe et al., 2006; Fisher, Aharon-Peretz, & Pratt, 2011; Rentrop et al., 2008). These disorders are thought to involve dysfunctions of frontal inhibitory processes, which can lead to increases in impulsive behavior. In line with these observations, a recent meta-analysis of 48 GNG imaging studies in controls revealed that two major foci of activation included the right middle frontal gyrus (MFG) and the ACC/pre-supplementary motor area (pre-SMA) region (Swick et al., 2011). Both of these frontal areas have been implicated in PTSD. Indeed, a group of civilian participants with PTSD showed an increase in false alarm errors in a GNG task and reduced activation in these same regions, relative to controls (Falconer et al., 2008).

The OEF/OIF patient population differs from many other populations because PTSD and mild TBI (mTBI) frequently co-occur. The estimated prevalence of this co-morbidity has ranged from 33% to 39% in the largest studies of OEF/OIF veterans (Carlson et al., 2011). Therefore, it is important to determine the extent of inhibitory control deficits in these patients, who are at increased risk for substance abuse and other impulsive behaviors (Jakupcak et al., 2009).

Studies in civilians with mTBI commonly observe executive dysfunction and memory impairments (Mathias, Beall, & Bigler, 2004), although these deficits tend to resolve within one to three months (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). There is considerable disagreement, however, in the characterization of mTBI as a minor contributor to post-deployment problems in OEF/OIF veterans (Sigford, Cifu, & Vanderploeg, 2009). Nonetheless, the overlap with PTSD symptoms is extensive (Stein & McAllister, 2009), and disentangling the effects of each has been challenging. It is becoming increasingly apparent that PTSD makes a substantial contribution to the persistent post-concussive symptoms (PCS) reported by OEF/OIF veterans (Hoge et al., 2008). In one recent study of 339 OEF/OIF veterans with positive mTBI histories, PTSD symptoms uniquely accounted for 46.6% of the variance

in self-reported PCS, while loss of consciousness accounted for only 1.6% (Lippa, Pastorek, Benge, & Thornton, 2010).

The cumulative impact of mTBI and PTSD on neurocognitive function has not been extensively explored in soldiers who have served in OEF and OIF, who are typically exposed to chronic stressors and threats to safety. Previous neuropsychological results in this population using standardized tests have been mixed, with some reporting deficits (Marx et al., 2009; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009) while others have not (Brenner et al., 2010; Gordon, Fitzpatrick, & Hilsabeck, 2011). However, no study has yet examined response inhibition in OEF/OIF veterans with mTBI and PTSD using the sensitive GNG task.

The current experiment tested veterans with PTSD and mTBI primarily due to blast injury, and veterans with PTSD only. Because our population had a paucity of OEF/OIF veterans with TBI but without PTSD, these individuals were excluded. Determining the effects of PTSD and mTBI on inhibitory control functions is critical to providing appropriate cognitive therapies and rehabilitation programs. After returning from Iraq and Afghanistan, many veterans face difficulties returning to work and maintaining relationships, even if deficits on standardized neuropsychological tests are not observed. Therefore, the development of more sensitive experimental designs is critical in evaluating potential tendencies toward impulsive behaviors.

The major question posed by the present study was whether OEF/OIF veterans with PTSD would show impairments in motor response inhibition. False alarm errors on NoGo trials were used as the primary measure of inhibitory control abilities. To manipulate the prepotency of responding, and hence the need for inhibitory control, the probability of Go to NoGo stimuli alternated between 50/50 ("easy") and 90/10 ("difficult") in different blocks. If the function of lateral and medial PFC regions is altered in the patients, one might predict that their performance in the GNG task would be impaired. Although the majority of patients (75%) had both PTSD and mTBI, a secondary question was whether the presence of a mild TBI would result in further deficits in those with PTSD.

Participants also completed standardized questionnaires to assess the severity of PTSD and depressive symptoms. We predicted that response inhibition performance would be related to scores on the PTSD checklist (PCL), with higher error rates in those with higher PCL scores. If the addition of a mild TBI is associated with a further decline in inhibitory control, then the combination of blast-related mTBI with PTSD could ultimately hinder recovery, from both the post-concussive symptoms and the psychiatric sequelae.

METHODS

Participants

The participants were 40 combat veterans diagnosed with PTSD (39 male, 1 female) and 33 age-matched veteran

Table 1. Demographic information and self-rating scores for the PTSD patients, the patient subgroups with and without mTBI, and the controls

	Patients (<i>n</i> = 40)	PTSD+mTBI (<i>n</i> = 30)	PTSD only (<i>n</i> = 10)	Controls (<i>n</i> = 33)
Age (yrs)	32.6 ± 7.5 (n.s.)	32.3 ± 7.5	32.6 ± 7.6	33.4 ± 8.1
Education (yrs)	13.3 ± 1.4 (***)	13.6 ± 1.2	13.2 ± 1.5	14.6 ± 1.6
Handedness	35 R, 3 L, 2 ambi	25 R, 3 L, 2 ambi	10 R	30 R, 3 L
Deployed (<i>n</i>)	40	30	10	19
Combat (<i>n</i>)	40	30	10	8
TBI events (<i>n</i>)	9 one, 21 > one	9 one, 21 > one	—	—
Type of injury	27 blast or both 3 nonblast	27 blast or both 3 nonblast	—	—
LOC	21; 5 dazed, 4 uncertain	21; 5 dazed, 4 uncertain	—	—
Years post	3.9 ± 1.6	3.8 ± 1.5	4.0 ± 2.2	—
Medications (<i>n</i>)	23	18	5	2
PCL-M	58.7 ± 12.1 (***)	59.4 ± 11.2	56.5 ± 14.9	27.3 ± 11.0
BDI	20.6 ± 9.9 (***)	20.0 ± 12.3	20.8 ± 9.2	6.1 ± 7.1

Note. The mean ± standard deviation are given for age, education, estimated years post-event(s), PCL-M, and BDI. The patient subgroups did not differ from each other for age, education, years post-event, PCL-M, and BDI.

n.s. = not significantly different from controls; *** Significantly different from controls at $p < .001$.

R = right; L = left; ambi = ambidextrous; LOC = loss of consciousness (of 30 patients with mTBI, 21 had LOC, 5 did not, and 4 were not sure whether they had LOC); Medications = number on psychoactive medications; PCL-M = post-traumatic stress disorder checklist, military version; BDI = Beck Depression Inventory; mTBI = mild traumatic brain injury.

controls (31 male, 2 female). Among the PTSD patients, 30 had sustained one or more mTBIs (primarily due to blast injury while serving in the military), while 10 had no history of mTBI (see Table 1 for details). Participants with evidence of significant medical disease, severe psychiatric problems (such as schizophrenia or bipolar disorder), active substance abuse, visual deficits, or history of other neurological events were excluded. Another 6 participants (4 patients, 2 controls) were initially enrolled, then excluded when additional information was revealed (childhood TBI; non-military PTSD; moderate TBI; other psychiatric disorder; not OEF/OIF). Most of the patients were identified and diagnosed in the TBI clinic of the consulting neurologist. A semi-structured clinical interview was conducted, and mild TBI was diagnosed based on patient self-report of the following criteria from the VA/DoD Clinical Practice Guidelines—loss of consciousness (LOC) 30 min or less or altered mental status (e.g., feeling dazed, disoriented, or confused), with post-traumatic amnesia less than 24 hr (The Management of Concussion/mTBI Working Group, 2009). PTSD diagnosis was based on semi-structured clinical interview using DSM-IV criteria. The diagnoses of mTBI and PTSD were corroborated with available VA medical records, to the fullest extent possible.

The diagnosis of PTSD was based on a review of the VA's Computerized Patient Record System (CPRS) for each enrolled patient. The initial PTSD diagnosis was made when the veteran sought help through the VA. The majority (36 of 40) were diagnosed by VA mental health providers. The presence of PTSD was confirmed by the consulting neurologist in 10 of these 36 patients upon entry into the study. One patient was diagnosed solely by the neurologist, and 3 patients were not enrolled in the VA system. A small number of participants were recruited from the local Vet Center, which provides services for PTSD but does not share diagnostic information with the VA.

Controls were recruited primarily through advertisements. Potential control subjects were screened for exclusionary criteria (described above) and history of mTBI or PTSD through an initial telephone interview, and further assessed at the first visit. Demographic information is shown in Table 1. The groups were matched for age but not education level. This could be due to the inability of many of the patients to return to school after their military service, and is typical of earlier studies on veterans with PTSD (e.g., McNally, Kaspi, Riemann, & Zeitlin, 1990; Vrana et al., 1995). However, another possibility is that low education serves as a risk factor for developing PTSD (Iversen et al., 2008; Larson, Booth-Kewley, Highfill-McRoy, & Young, 2009); thus, those with lower educational attainment were at greater risk for PTSD. Level of education did not influence the outcome, however, as will be discussed in the Results section.

Wechsler Test of Adult Reading (WTAR) data (Wechsler, 2001) were available for a subset of the participants (14 patients and 17 controls). The estimated full-scale IQ (FSIQ) did not differ between the groups [$t(1,29) = 1.44$; $p = .16$], who were well-matched and representative of the entire sample (Table 2).

English was the primary language for all participants. The subjects signed informed consent statements approved by the Institutional Review Board of the VA Northern California Health Care System and were paid for their participation. All procedures were in compliance with the Declaration of Helsinki.

Go-NoGo Task

We implemented the experimental design used in a previous study on patients with frontal lobe lesions (Swick et al., 2008). Stimuli consisted of single uppercase letters printed in a large black font (248 pt) on a white background. The stimuli

Table 2. Demographic information, self-rating scores, estimated full-scale IQ based on Wechsler Test of Adult Reading (WTAR) scores, and NoGo errors in the GNG task for a subset of the participants

	Patients (<i>n</i> = 14)	Controls (<i>n</i> = 17)
Age (yrs)	36.0 ± 8.5 (n.s.)	35.2 ± 8.8
Education (yrs)	13.8 ± 1.2 (n.s.)	14.6 ± 2.0
PCL-M	57.0 ± 13.0 (***)	27.9 ± 10.0
BDI	20.4 ± 8.6 (***)	5.4 ± 5.4
FSIQ (est.)	101.6 ± 11.1 (n.s.)	106.8 ± 9.2
50/50 errors	14.0 ± 8.6 (***)	6.1 ± 3.2
90/10 errors	45.9 ± 17.4 (***)	22.9 ± 12.2

Note. The mean ± standard deviation are given for age, education, PCL-M, and BDI. n.s. = not significantly different from controls; *** significantly different from controls at $p \leq .001$.

PCL-M = post-traumatic stress disorder checklist, military version; BDI = Beck Depression Inventory; GNG = Go/NoGo task; FSIQ = full-scale IQ.

were presented on a 16 inch ViewSonic monitor using a PC that ran Presentation® software (Neurobehavioral Systems, Inc., <http://www.neurobs.com/>). Stimuli were rapidly and serially presented at the center of a computer screen for 200 ms duration once every 1500 ms. Subjects were instructed to respond as quickly as possible to every letter except for “X” by pressing a button on the keyboard with the index finger of the dominant hand. In four separate blocks of trials, the proportion of “Go” to “NoGo” trials alternated between 50/50 and 90/10. There were 140 trials per block, with short rest breaks between each block. A short practice set of 30 trials (15 Go and 15 NoGo, randomly intermixed) preceded the experimental trials.

Questionnaires

At the end of the session, all subjects completed three self-report questionnaires: the Barratt Impulsiveness Scale (BIS), the PTSD Checklist, Military Version (PCL-M), and the Beck Depression Inventory (BDI). The BIS is a 30-item self-report measure thought to assess the personality construct of “impulsiveness” (Patton, Stanford, & Barratt, 1995). Results from the BIS will be reported in a separate publication. The PCL-M for DSM-IV (Weathers, Litz, Huska, & Keane, 1994) is an accepted diagnostic tool for measuring PTSD (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). The PCL-M is a 17-item self-report tool that establishes the presence and degree of PTSD symptoms in military personnel. It has three clusters or subsets: re-experiencing, numbing, and hyperarousal. PTSD is indicated in a veteran population with a score of 50 or greater (Forbes, Creamer, & Biddle, 2001). The PCL-M score of one control participant who had not yet sought clinical care placed them in the PTSD group. This individual was subsequently diagnosed with PTSD by a psychiatrist. Another veteran recruited via an advertisement initially self-identified as having PTSD but had a low score on the PCL-M. Omitting these two

individuals did not affect the results, so they are included in all analyses. In addition, a clinical neuropsychologist reviewed information from both patients and determined that their PCL scores reflected current symptomatology (or lack thereof). The BDI is one of the most commonly used self-report screens for major depressive disorder (MDD) and has been validated with well-established psychometric properties (Beck, Steer, & Gabin, 1988). The BDI is a 21-item test which measures the presence and degree of depression in adolescents and adults.

Data Analysis

Error data were characterized as missed responses to Go stimuli and false alarm responses to NoGo stimuli. The mean reaction time (RT) was calculated for each subject and sorted into correct responses to Go stimuli and incorrect responses to NoGo stimuli. Statistical analyses were carried out using repeated measures analyses of variance (ANOVAs) with factors of group (patients, controls) and probability (50/50, 90/10). Secondary analyses compared patients with mTBI and PTSD to those with PTSD only. The correlations between self-report measures and errors in the difficult 90/10 condition were determined using the Spearman rank-order statistic, with a Bonferroni correction for multiple comparisons ($p < .005$). Effect sizes are reported as partial eta-squared (η_p^2) for ANOVA and Cohen’s d for follow-up comparisons.

RESULTS

Accuracy

An initial ANOVA with factors of group (controls, patients), probability (50/50, 90/10), and error type (misses, false alarms) revealed that every main effect and interaction was highly significant, including group \times error type [$F(1,71) = 26.11$; $p < .0001$; $\eta_p^2 = .26$]. Thus, separate ANOVAs were performed for errors of omission on Go trials (misses) and errors of commission on NoGo trials (false alarms). In general, the rate of misses was very low and did not differ by probability ($p = .19$). The percentage of missed responses for the 50/50 and 90/10 probability conditions was 0.65% and 0.28%, respectively, for controls; and 1.93% and 1.55% for patients. Although floor effects are a concern, the percentage of misses was greater in the patients than in controls [$F(1,71) = 5.20$; $p = .03$; $\eta_p^2 = .07$], which did not interact with probability ($p > .9$).

In contrast, NoGo errors (Figure 1, top) showed a highly significant effect of group [$F(1,71) = 26.44$; $p < .0001$; $\eta_p^2 = .27$], probability [$F(1,71) = 93.97$; $p < .0001$; $\eta_p^2 = .73$], and an interaction between the two [$F(1,71) = 14.03$; $p = .0004$; $\eta_p^2 = .17$]. The PTSD patients made more false alarm errors than controls for both the 50/50 [$F(1,71) = 22.83$; $p < .0001$; $d = 1.12$] and the 90/10 [$F(1,71) = 23.35$; $p < .0001$; $d = 1.14$] probability conditions. Although the effect sizes are nearly

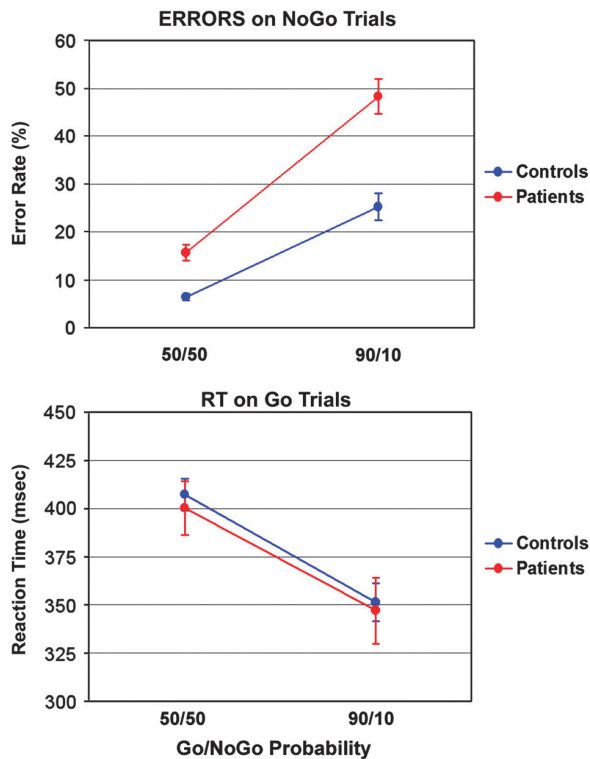


Fig. 1. Top: False alarm errors (percentage of NoGo errors) for the patients ($n = 40$) and controls ($n = 33$) in the easy (50/50) and difficult (90/10) conditions. **Bottom:** Reaction times (RTs) on correct Go trials (in milliseconds) in the easy (50/50) and difficult (90/10) conditions. The error bars depict standard errors.

equivalent, the significant interaction suggests the patients' difficulty with inhibiting inappropriate responses was exacerbated in the difficult 90/10 condition, when responding was prepotent. A secondary ANOVA was conducted to compare PTSD patients with and without mTBI (Figure 2), revealing that patients with both PTSD and mTBI did not differ from those with PTSD only. The main effect of group [$F(1,38) = 0.2$; $p = .89$] and the group by probability interaction [$F(1,38) = 0.2$; $p = .88$] were not significant.

Reaction Times

The initial comparison examined RTs on correct Go trials only (Figure 1, bottom), and revealed no differences between the patients and controls in the speed of responding ($p > .7$). All subjects were faster to respond to targets in the 90/10 condition than in the 50/50 condition, which was reflected in a highly significant main effect of probability [$F(1,71) = 200.59$; $p < .0001$]. Probability did not interact with group ($p > .7$). The secondary analysis showed that patients with both PTSD and mTBI did not differ from those with PTSD only ($p > .7$).

An additional ANOVA compared response times for correct and error trials. All participants had faster RTs on incorrect NoGo trials ($308 \text{ ms} \pm 70 \text{ ms}$) than on correct

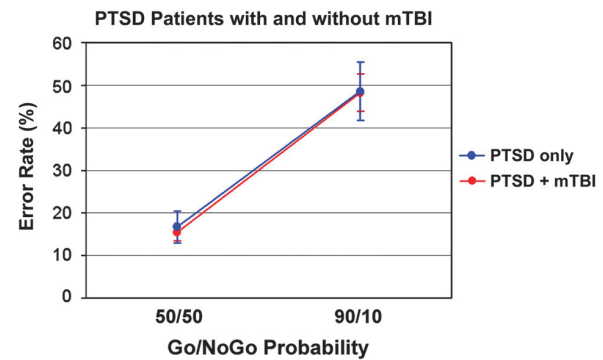


Fig. 2. False alarm errors (percentage of NoGo errors) for patients with both mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD; $n = 30$) and patients with PTSD only ($n = 10$) in the easy (50/50) and difficult (90/10) conditions. The error bars depict standard errors.

Go trials ($376 \text{ ms} \pm 86 \text{ ms}$), suggesting that impulsive responding led to the majority of errors in performance. This result was indicated by a main effect of accuracy [$F(1,70) = 479.30$; $p < .0001$]¹ that did not interact with group ($p > .3$). This speeding up on error trials was numerically greater for the 50/50 condition (80 ms) than for the 90/10 condition (57 ms), as indicated by the probability by accuracy interaction [$F(1,70) = 11.28$; $p = .001$].

Correlations Between Experimental and Self-Report Measures

The associations between scores on the self-report questionnaires and false alarm errors in the difficult 90/10 condition were determined using Spearman Rank Correlations (corrected at $p < .005$). Scores on the PCL-M and BDI showed a strong correlation with performance: more severe levels of PTSD symptoms ($\rho = .52$; $p = .0001$) and depression ($\rho = .53$; $p < .0001$) were both associated with higher error rates. All three PTSD symptom clusters produced a correlation with error rates: re-experiencing ($\rho = .54$; $p < .0001$), avoidance/numbing ($\rho = .47$; $p < .0001$), and hyperarousal ($\rho = .49$; $p < .0001$). However, when these three variables were entered into a standard multiple regression analysis to control for shared variance (see Vasterling et al., 1998), re-experiencing was the only significant predictor of errors in the 90/10 condition ($p = .02$; see Table 3). Finally, a striking correlation between PCL-M and BDI scores was observed ($\rho = .90$; $p < .0001$), indicating that PTSD and depression symptoms showed a high level of co-morbidity in these OEF/OIF veterans. As clearly expected based on clinician diagnosis, the patients reported higher PCL-M and BDI scores than the control group, but there were no differences between PTSD patients with and without mTBI (Table 1).

¹ There is one less degree of freedom in the denominator because one control subject did not have any errors in the 90/10 condition.

Table 3. Relationship of false alarm errors in the 90/10 condition to the three PTSD symptom clusters, based on self-reported PCL-M scores

Symptom cluster	B	Std. Error	β	<i>t</i>	<i>p</i>
Re-experiencing	1.822	.748	.478	2.435	.018
Avoidance/numbing	-.131	.586	-.048	-.224	.823
Hyperarousal	.487	.787	.135	.619	.538

Note. $R = .557$; Adjusted $R^2 = .281$; $F(3,69) = 10.36$, $p < .0001$.

PTSD = post-traumatic stress disorder; PCL-M = post-traumatic stress disorder checklist, military version.

Effects of Education, Estimated IQ, Diagnostic Certainty, and Medications

Two additional analyses established that the patients' deficits in accuracy were unrelated to education level. In the first, the less educated half of the control group ($n = 17$) was compared to the entire patient group (now matched for education: 13.4 vs. 13.3 years, respectively). The same results for false alarm errors were obtained: a main effect of group [$F(1,55) = 14.27$; $p = .0004$], and an interaction between group and probability [$F(1,55) = 6.72$; $p = .01$]. In the second, the groups were more closely matched in number. We compared the lower educated half of controls ($n = 17$) to the upper half of patients ($n = 20$), so now the patients were significantly more educated (13.4 vs. 14.3 years, respectively; $p = .001$). Again, the same impairment was observed in the patients: a main effect of group [$F(1,35) = 14.01$; $p = .0007$], and an interaction between group and probability [$F(1,35) = 7.55$; $p = .009$].

Thus, group differences in education level did not influence the outcome. Another question is whether there were group differences in IQ which might have affected the results. WTAR data were available for a subset of the participants to provide an estimate of pre-morbid IQ (Wechsler, 2001). As reported previously, the estimated FSIQ did not differ between the groups, who were well-matched and representative of the entire sample (Table 2). This subset of patients made significantly more false alarm errors than controls for both the 50/50 and 90/10 conditions ($p's \leq .001$). Furthermore, errors on the 90/10 condition were not at all correlated with estimated FSIQ ($r = .017$; $p = .92$).

Although the PCL-M was not used for diagnostic purposes, eight patients with a formal diagnosis of PTSD from semi-structured clinical interview had scores below 50 (range, 31–49) on the day they were tested. Removing these patients and any other clinically discrepant participants from the analyses did not affect the results ($p's \leq .0001$ for false alarm errors in both the 50/50 and 90/10 conditions), nor did it change group demographics (mean age for all 40 patients = 32.6 years and for 32 patients = 32.6 years; mean education for all 40 patients = 13.3 years and for 32 patients = 13.1 years).

To examine the effects of prescription drugs on performance, the 23 patients taking psychotropic medication(s) of any class (sedative/hypnotics, antidepressants, mood stabilizers, atypical

antipsychotics, opioids, or alpha adrenergic blockers) were compared to the 17 patients who were not. Medication use did not affect RTs (main effect $p = .20$ and interaction $p = .11$, with the trend being faster RTs in those taking medications) or NoGo error rate (main effect $p = .28$ and interaction $p = .31$).

Role of Deployment, Loss of Consciousness, and Number of Events

Among the veterans in the control group, 19 of 33 were deployed. An additional ANOVA compared these deployed controls ($n = 19$) to the patients ($n = 40$) for NoGo errors. Results were similar to the main analysis: a highly significant effect of group [$F(1,57) = 14.13$; $p = .0004$] and a group by probability interaction [$F(1,57) = 6.56$; $p = .01$] were observed.

As stated earlier, the secondary analysis comparing PTSD patients with and without mTBI found no differences in performance. However, the definition of mTBI includes individuals with altered mental status but no loss of consciousness (LOC). Self-reported LOC occurred in 21 of 30 patients with mTBI. To examine whether PTSD+mTBI patients with self-reported LOC ($n = 21$) might differ from those with PTSD only ($n = 10$), another ANOVA was run. Again, there were no significant main or interactive effects of group (both $p's > .9$). Finally, the group with mTBI was restricted further to those with both LOC and more than two events ($n = 15$), and compared to the PTSD only group. These two patient subgroups did not differ significantly in their PCL-M scores (59.1 vs. 56.6 respectively; $p = .62$). There were still no differences for NoGo errors (main effect of group, $p > .9$; interaction: $p > .8$).

DISCUSSION

The present study demonstrated that OEF/OIF veterans with PTSD were impaired at inhibiting inappropriate motor responses. A speed-accuracy trade-off could not account for this result, as RTs in the patient and control groups were virtually identical. As well, the severity of PTSD and depressive symptoms were both highly correlated with performance. These results suggest that response inhibition is compromised in participants with PTSD, which is consistent with previous results in civilians (Falconer et al., 2008; Wu et al., 2010) and Gulf War veterans (Vasterling et al., 1998). A deficit in inhibitory control could have detrimental effects on daily activities such as driving (Lew, Amick, Kraft, Stein, & Cifu, 2010), and may hinder recovery from traumatic events (Aupperle et al., 2012).

In addition, the inhibitory control deficit occurred whether or not the patient had reported a mild TBI in addition to PTSD. Although this finding is preliminary, the fact that mTBI did not add to the cognitive deficits seen in those with PTSD suggests that in the current population, where loss of consciousness was brief (less than 1–2 min in most patients) and where no clear LOC occurred in 30% (with dazed/altered mental status),

PTSD was the primary driver of performance. Further restriction of the mTBI group to those with self-reported LOC and more than two events did not alter this outcome. Furthermore, the severity of PTSD symptoms did not differ in patients with and without mTBI, in agreement with Romesser and colleagues (2011). There has been considerable controversy over the diagnosis of mTBI in OEF/OIF veterans, with some questioning the impact of mTBI on post-deployment functioning relative to PTSD, depression, and other psychiatric disorders (e.g., Hoge et al., 2008; Hoge, Goldberg, & Castro, 2009). Results could differ in military personnel with more “severe” mTBIs, such as those with a combination of blast injury and secondary head trauma, for example, the group of U.S. military personnel airlifted to Landstuhl Medical Center in Germany (Mac Donald et al., 2011). Those subjects showed evidence of white matter abnormalities on diffusion tensor imaging (DTI) scans.

On a related note, the co-morbidity between PTSD and depression symptoms was striking, with a very high correlation between the severity of self-reported symptoms on the two scales. Although the two disorders share the overlapping construct of negative affect, the symptom cluster of re-experiencing is unique to PTSD (Cloitre, Koenen, Gratz, & Jakupcak, 2002). Increased scores on both the BDI and the PCL-M were strongly associated with a higher percentage of false alarm errors in the difficult condition. All three PTSD symptom clusters (re-experiencing, avoidance/numbing, and hyperarousal) were correlated with performance individually, but when entered into a multiple regression, re-experiencing was the only significant predictor of error rate. This finding replicates Vasterling et al. (1998) and suggests that the symptom cluster most unique to PTSD was specifically related to the decline in inhibitory control.

The strong correlation between PCL-M scores and error rates is in agreement with previous results. Falconer and colleagues (2008) also found a positive correlation between false alarm errors and PTSD severity as measured by the Clinician-Administered PTSD Scale (CAPS). In their imaging study, civilian PTSD patients showed reduced activity in the right lateral PFC and the ACC/pre-SMA regions relative to controls. Furthermore, more severe PTSD symptoms were associated with less activation in bilateral PFC and medial frontal areas in the patients (Falconer et al., 2008). This is in accord with what would be predicted on the basis of meta-analytic studies of the GNG task in controls (Swick et al., 2011), because those regions were uniformly recruited for response inhibition across a large number of experiments. The activation foci showing the greatest overlap across GNG imaging studies included the right anterior insula and right MFG (e.g., Zheng, Oka, Bokura, & Yamaguchi, 2008) and dorsomedial areas such as the SMA, pre-SMA, and ACC (e.g., Li, Huang, Constable, & Sinha, 2006; Mostofsky & Simmonds, 2008). As mentioned previously, individuals with PTSD have smaller ACC volumes (Hamner, Lorberbaum, & George, 1999; Rauch et al., 2003; Woodward et al., 2006). It is now becoming more apparent that dorsolateral PFC function may be compromised in PTSD

as well (Aupperle et al., 2012; Simmons & Matthews, 2012). Difficulties in recruiting the MFG during a cognitive task were associated with higher levels of PTSD symptoms (Morey et al., 2008).

Disentangling the effects of mTBI, PTSD, and depression on cognitive performance and brain function has not been a straightforward endeavor. In a structural imaging study of individuals with both PTSD and depression, common areas of volume reduction were located in the PFC (Kroes, Rugg, Whalley, & Brewin, 2011). An fMRI study demonstrated that veterans with both mTBI and MDD showed greater activity in the amygdala, and less activity in dorsolateral PFC, than veterans with mTBI only during an emotional face matching task (Matthews et al., 2011).

Robertson, Manly, Andrade, Baddeley, and Yiend (1997) have argued that in addition to motor response inhibition, the Go/NoGo task is a measure of sustained attention. Both motor response inhibition and/or lapses of attention can produce high NoGo error rates. In our experiment, the 90/10 blocks might have been more monotonous than the 50/50 blocks, so sustained attention was required to a greater degree in the former. Thus, it is noteworthy that the patients showed substantially elevated false alarm rates in both conditions. In addition, omitted responses on Go trials were not greatly increased (mean of 1.7% in the patients), as might be expected if distractibility and sustained attention had been the primary difficulties. Although a significant difference was observed, this finding should be interpreted with caution because the controls showed a floor effect, with the rate of misses below 1%. Finally, the pattern of RTs on correct Versus incorrect Go trials indicated that errors were due to impulsive responding. Therefore, an inhibitory control deficit remains the best explanation for the patients' performance.

Previous Go/NoGo results in TBI patients with moderate to severe injuries have been mixed, but a recent meta-analysis of 20 response inhibition studies in adults found a moderate effect size (Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011). Although many papers have reported deficits (e.g., Robertson et al., 1997), others have not (Swick et al., 2008; Whyte, Grieb-Neff, Gantz, & Polansky, 2006). Our prior study demonstrated that patients with severe TBIs and large bilateral lesions in the orbitofrontal cortex were not impaired on the GNG task (Swick et al., 2008). On the other hand, stroke patients with focal lesions in the left inferior frontal gyrus and left anterior insula showed a pattern of impairment similar to that reported here (Swick et al., 2008). However, the present group of OIF/OEF veterans had an even greater deficit in motor response inhibition, which can have important implications for daily life. Since performance did not differ in patients with and without mTBI, these results suggest that PTSD symptoms interfere with effective response inhibition.

The present study has several limitations. PTSD was diagnosed by semi-structured clinical interview instead of the CAPS, which is considered the “gold standard” (Blake et al., 1995). Nonetheless, a strong correlation between false alarm errors and PCL-M scores was observed, suggesting a

relationship between inhibitory control deficits and self-reported PTSD symptom severity that was independent of formal diagnosis. Furthermore, there is a very high correlation between the PCL and the CAPS: diagnostic efficiency of the PCL is 0.900 versus the CAPS (Blanchard et al., 1996). The difficult issue of making an accurate mTBI diagnosis pertains to most veterans of OEF/OIF, as it is dependent on recollection and self-report. Medical records from Iraq and Afghanistan were not available for the patients, as they had no medical treatment at the time. Brief losses of consciousness or altered mental status may not always be caused by blast exposure itself, but can be due to acute stress, confusion, or sleep deprivation (Hoge et al., 2009). Nevertheless, all current participants with mTBI were diagnosed by a neurologist.

Other limitations include the fact that the control veterans were not all deployed or exposed to combat. Future studies should attempt to better match the groups on these factors, as deployment and combat exposure may have detrimental effects on their own. However, an analysis restricted to only those controls who were deployed revealed that the patients were still impaired relative to this group. The controls and patients were not matched for years of education, although subgroup analyses convincingly demonstrated this did not affect the pattern of results. Since all patients were highly motivated to participate in the study, we did not believe that effort was an issue. However, we did not use a measure of effort or malingering to verify this. Another difficult issue is separating the effects of PTSD and depressive symptoms on cognitive performance (Cloitre et al., 2002), due to their high co-morbidity in this population. The current study was not designed to address this question. The recruitment and selection of patients was not completely random, but was primarily focused on those who attended a specialty TBI clinic. Additional efforts were made to recruit from mental health clinics and veterans organizations as well. However, there were fewer patients with PTSD only, so the comparisons between this group and the mTBI + PTSD group were low in power. Finally, due to the difficulty of finding patients with pure mTBI in isolation from PTSD, we were not able to include this population in the current study. Inclusion of this group in future studies will allow stronger conclusions about the effects of mTBI on response inhibition.

CONCLUSIONS

The present results indicated that OEF/OIF veterans with PTSD were impaired at inhibiting motor responses in a Go/NoGo task. The inhibitory control deficit was exacerbated when responding was more prepotent, suggestive of more impulsive responding in the patients. False alarm error rates were strongly correlated with self-reported symptoms of PTSD and depression. Furthermore, the combination of mTBI and PTSD did not result in worse performance than PTSD alone in the present population. Taken together, the current findings suggest that OEF/OIF veterans with PTSD show impairments in response inhibition. Additional studies

are needed to verify that these findings are independent of mTBI. Since neurocognitive impairments may hinder the effectiveness of PTSD therapies that rely on cognitive reappraisal and disengagement from traumatic stimuli (Aupperle et al., 2012; Vasterling & Verfaellie, 2009), incorporating treatments that strengthen executive functions might be considered in the future.

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Post-traumatic stress disorder is associated with limited executive resources in a working memory task

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Background: The goal of the current experiment was to examine the extent of central executive impairments in patients with post-traumatic stress disorder (PTSD). A dual-task design was used to determine if cognitive impairment in working memory was linked to executive control limitations by examining performance on a WM task alone and when a secondary attention task was performed during the maintenance period.

Methods: Participants performed a Sternberg working memory task in which either one or four items were presented. After a brief maintenance period, a probe was presented and participants indicated whether or not the probe was a member of the previous memory set. In a single-task condition, the Sternberg task was performed on its own. In a dual-task condition, the maintenance period was filled with an arrow flanker task in which participants responded quickly to a central arrow surrounded by distracting arrows. Both behavioral and electrophysiological data were collected.

Results: Behavioral analysis found a significant group by task interaction, indicating that PTSD patients were less accurate on the working memory task than the controls, especially in the dual task condition. Electrophysiological results indicated that both the PTSD group and the controls showed similar brain patterns from 300 ms to 500 ms when differentiating old and new probes in the single task condition. However, when taxed with the additional flanker task during the maintenance period, the ERPs of the PTSD group no longer differentiated old and new probes. This lack of differentiation reflects impaired WM performance under more difficult dual task conditions.

Conclusions: Exacerbated difficulty in performing a WM task with concurrent task demands suggests executive control dysfunction in PTSD. We suggest that the dual task design used here is an ecologically valid measure that captures the real-world difficulties in multitasking that

some individuals with PTSD report. Such experimental measures may prove important in evaluating effectiveness of rehabilitation treatments.

Introduction

Limitations in executive control can lead to impairments in multiple aspects of cognition. Executive control coordinates and manipulates information held in working memory, switches attention from one representation to another, inhibits pre-potent responses, maintains sequences of events, and monitors performance (Baddeley, 1996). Individuals with post-traumatic stress disorder (PTSD) often show impairments in coordinating, inhibiting, and monitoring cognition and behavior (Swick et al., 2012; Vasterling et al., 1998). However, the effects of PTSD on executive function have not been as well-documented as difficulties in regulating emotional memory and fear learning (Koso & Hansen, 2006; Leskin & White, 2007; Vasterling et al., 1998). Task performance on emotionally-neutral stimuli in PTSD patients has shown mixed results. Some studies report deficits in verbal working memory (WM) tasks (Elzinga & Bremner, 2002; Vasterling et al., 1998), while other studies show little to no impairment on performance (Golier et al., 1997; Neylan et al., 2003). Researchers suggest that the inconsistent results may be linked to varying levels of attention (Neylan et al., 2003), which would be reflected in tasks examining executive control. The current experiment set out to determine if cognitive impairment in WM is linked to executive control limitations by examining performance on WM task alone and when a secondary attention task is performed during the maintenance period. Exacerbated difficulty in performing a WM task with concurrent task demands would suggest executive control dysfunction in PTSD rather than a general decline in memory (Baddeley, 1996).

PTSD symptomatology is often related to cognitive dysfunction. Previous research suggests that PTSD symptoms are specifically related to the decline in attentional control and memory performance (Bremner et al., 1993; Elzinga & Bremner, 2002; Swick et al., 2012;

Vasterling et al., 1998). Bremner et al. (1993) found a significant decline in both immediate and delayed recall performance in patients with PTSD compared to military controls using the Wechsler Memory scale. PTSD symptoms such as hyperarousal and intrusive memories contribute to everyday problems, such as difficulty concentrating and remembering day-to-day tasks (Koenen et al., 2001). The impairment in WM performance is strongly correlated with symptom severity of re-experiencing the traumatic event (Elzinga & Bremner, 2002). In addition, other neuropsychological tests indicate that re-experiencing is also significantly related to impairments in inhibitory control (Swick et al., 2012; Vasterling et al., 1998).

Although some studies suggest impaired performance on attention, learning acquisition, and memory performance (Bremner et al., 1993; Vasterling et al., 1998), other research has shown varying levels of cognitive impairment (Brenner et al., 2010; Golier et al., 1997). Some researchers have suggested that the inconsistency in cognitive performance results may be related to fluctuating levels of attention and concentration (Brenner et al., 2010; Neylan et al., 2003). Inconsistent task performance may be an indicator of executive dysfunction (e.g. Stuss et al. 2003). The central executive component (CES) of Baddeley's (1996) working memory model is thought to regulate attentional resources and control the maintenance and manipulation of two other components, the visuospatial sketchpad and phonological loop. Deficits in the CES are more pronounced on complex, novel tasks and dual task processing due to the limited capacity of the CES (McDowell et al., 1997). Therefore, the link in uncovering cognitive difficulty in patients with PTSD may not necessarily be apparent when just testing one cognitive domain (e.g. verbal fluency), but might instead be more prominent in tasks that require executive control.

The executive control component is thought to be generated in parts of the prefrontal cortex (PFC) (McDowell et al., 1997; Smith et al., 1998; Wager & Smith, 2003). Patients with frontal lobe damage may perform well on certain cognitive tasks, specifically on tasks that do not require coordinating performance, but are unable to coordinate multiple processes as evidenced by declines in dual task performance (Baddeley, 1996; Dreher et al., 2008). This may be a critical issue for detecting impairment in PTSD patients. Indeed, other research has compared PTSD patient's patterns in performance to patients with frontal lobe injury (Vasterling et al. 1998). In addition, both patients with frontal lobe damage and patients with PTSD often complain of problems manifesting in complex situations that require structure and the coordination of events and goals, such as shopping or studying for an exam (Shallice & Burgess, 1991). Previous results indicate that dual-task performance may be sensitive to evaluate "real-world" level functioning (McDowell et al., 1997), but no studies have examined dual task performance in PTSD. Here, we focus on WM retrieval and how it is affected by the performance of a demanding visual attention task during the retention interval.

To determine whether behavioral deficits in PTSD patients are accompanied by neurophysiological changes, we also examined event-related potentials (ERPs) to WM retrieval and how electrophysiological changes are affected by a demanding visual attention task during the retention interval. ERP studies have implicated impaired cognitive performance in PTSD patients by examining the amplitude and latency of specific time-locked components that reflect attention and memory updating processes. Many researchers have employed an oddball task to examine abnormalities in target detection and context updating in PTSD patients (Galletly et al., 2001; Javanbakht et al., 2011; Karl et al., 2006; Veltmeyer et al., 2009). The majority of studies have reported an attenuated P300 response to target stimuli (Galletly et al., 2001; Veltmeyer et

al., 2009), However, neuropsychological measures of WM performance are not correlated with the amplitude or latency of the P300 (Walhovd & Fjell, 2001). Therefore, a new approach is needed to examine electrophysiological changes related to WM deficits.

A specific neural marker of memory retrieval processes is the ERP old/new effect. This electrophysiological response consists of a positive shift in the waveform to previously presented items that are correctly recognized, relative to new items that are correctly rejected (Rugg & Curran, 2007). Although typically examined using experimental designs such as study/test list learning (Rugg & Curran, 2007) and continuous recognition (Swick & Knight, 1997), the old/new effect has also been examined in WM and Sternberg tasks (Tays et al., 2008, 2011). In those studies, an array of letters or words was presented, followed after a delay by a probe stimulus. A probe that was contained within the array (“old”) elicited a greater positivity from approximately 350 to 600 ms than a probe that was not in the array (“new”).

Thus far, no studies have examined ERP old/new effects in PTSD patients, either under single or dual task conditions. In addition to examining verbal WM performance, the present study incorporated a distracting secondary task to tax executive control processes while maintaining a high or low WM load. We predicted that PTSD patients would show a decline in WM performance, especially in the dual task condition. Electrophysiological measures were expected to reflect this decline in performance by showing a reduction in the amplitude of the old/new effect in the dual task condition. We also predicted that behavioral accuracy and ERP measures would be correlated with PTSD symptom severity.

Methods

Participants

Participants were 18 combat (17 male, 1 female) OIF/OEF veterans diagnosed with PTSD and 16 (15 male, 1 female) demographically-matched controls. One combat veteran in the PTSD group was unable to complete the experiment and was subsequently dropped from analysis leaving the PTSD group at $n=17$ (16 male, 1 female). Fourteen of the participants with PTSD had attended a clinic for traumatic brain injury (TBI); however, all participants reported no history of TBI involving loss of consciousness greater than five minutes (Shin et al., 2009), or any other pre-existing neurological disease. PTSD diagnosis was confirmed via review of electronic medical charts. The groups did not significantly differ in age (PTSD: mean age 33 ± 7 years; and Military Controls: mean age 36 ± 7 years), ($F(1,31) = 1.462$, $p=0.236$). However, there were significant group differences for education (PTSD: mean years of education: 13.68 ± 1.10 ; Military Controls: 14.94 ± 1.95), ($F(1,31) = 10.366$, $p=0.003$). We addressed this by including education as a factor in correlation measures of any significant group differences. Both the PTSD and military control group were enrolled into the study in parallel.

All participants enrolled reported no history of other psychological disorders (excluding depression and general anxiety, due to the high comorbidity rate with PTSD, or significant substance abuse. The experimental protocol was approved by the Institutional Review Board of the VA Northern California Health Care System (VANCHCS), and all participants gave informed consent prior to beginning the experiment. They were paid for transportation expenses plus \$20/hour for their participation. All participants had been previously enrolled in an ongoing research project at the VANCHCS.

Stimuli and Tasks

Single Task Condition (Sternberg Memory Task): In the single task condition, participants were required to perform a Sternberg memory task. Participants were seated in a darkened, sound-attenuated room and were instructed to fixate at the center of a screen, blinking as little as possible. Participants were shown either one consonant (presented for 2000 ms) or a set of four consonants (presented for 3500 ms), which they were asked to remember. After a delay of 8500 ms, another consonant was presented (the probe). Participants responded with a button press to indicate whether or not the probe was part of the memory set. For each trial, the set size (1 or 4) as well as the probe type (old or new) was determined randomly with equal probabilities. There were 10 blocks of 10 trials each, for a total of 100 trials.

Dual Task Condition (Sternberg Memory Task + Arrow Flanker): In the dual task condition, participants were required to perform an additional arrow flanker task during the delay interval of the Sternberg memory task just described. Nine flanker trials began 300 to 500 ms following the presentation of each Sternberg memory set. Participants were instructed to respond with a button press to indicate, as quickly and accurately as possible, whether each central arrow pointed to the left or the right. Flanking arrows, positioned either above, below, or both above and below the central arrow, could point in either the same (congruent) direction (40 percent of trials) or different (incongruent) direction (60 percent of trials). Each flanker stimulus was presented for 200 ms, with the next trial beginning 600 to 800 ms after a response was made. If there was no response, the next trial began after 900 ms. The Sternberg probe was then presented 500 ms following the final flanker trial, and participants responded with a button press to indicate whether this item was in the previous memory set. Other parameters were as described above. Each of the ten blocks contained 10 Sternberg trials, each with 9 flanker trials embedded during each delay interval, for a total of 100 Sternberg trials and 900 arrow flankers.

A single task version of the arrow was also presented during the session, which will be reported elsewhere. Each participant completed all three tasks, with task order counterbalanced. The total test time was approximately two hours.

EEG Recording

Continuous EEG was recorded from 64 scalp electrodes and two electrodes placed on the left and right mastoids using the ActiveTwo Biosemi electrode system. Four electrodes placed laterally and below the right and left eyes recorded blinks and eye movements. The EEG was sampled at 512 Hz. Off-line analysis was completed using Brain Vision Analyzer software. Data were re-referenced to the average of the mastoid electrodes and bandpass filtered from 0.1 to 30 Hz. The EEG was segmented for each trial beginning 100 ms pre-stimulus and extending to 900 ms post-stimulus onset. EEG was corrected for blinks; eye movements and extraneous artifacts exceeding 150 microvolts were rejected.

Statistical Analysis

Behavioral Performance: Behavioral analyses examined the effect of reaction time (RT) and accuracy using repeated measure ANOVAs. Only correct responses to Sternberg probe were used in the RT analysis. The RT data for the Sternberg was analyzed using a 2 X 2 X 2 factor design: Task (single or dual), Set Size (1 or 4), Probe (old or new) and Group as the between subject factor (PTSD or military control). The accuracy data analyzed the percentage of correct responses using the same factor design as the RT analysis. Follow-up paired t-test comparisons investigated significant interactions.

Electrophysiological Analysis: The later old/new effect was analyzed in 100 ms intervals. Pelosi et al. (1998) argued that due to shifts in amplitude for memory processing, mean amplitude measures over the later portion of the wave are more indicative of memory processing.

Experimental effects on ERPs time-locked to the onset of the Sternberg probe were analyzed by taking the mean amplitude of six midline electrodes over time windows of 300-400 ms, 400-500 ms, 500-600 ms, and 600-700 ms, with the factors Task (single or dual), Set Size (1 or 4), Probe (old or new), Electrode (Fz, FCz, Cz, CPz, Pz, or POz) and Group (controls or PTSD). These intervals were selected to capture the sustained old/new effects of the Task manipulation that were observed beginning around 300 ms following the presentation of the probe. To ensure that each averaged ERP represented at least 40 artifact-free segments, effects of Set Size were examined in analyses that collapsed across Probe, and effects of Probe were examined in analyses that collapsed across Set Size.

Results

Behavioral Results

The participants with PTSD were less accurate than controls on the Sternberg working memory task, and their performance suffered to a greater extent in the dual task condition (Fig. 1). This was supported by a main effect of Group [$F(1,31)=5.55, p=0.03$] and a Task by Group interaction [$F(1,31)=4.42, p=0.04$]. The PTSD patients performed marginally worse than controls in the single task condition [$F(1,31)=2.49, p=.12$] but were significantly less accurate on the Sternberg task in the dual task condition [$F(1,31)=6.42, p=0.02$], when the demanding flanker task occurred during the working memory delay (Fig. 1). In addition, all participants were less accurate in the dual task compared to the single task, and for new probes compared to old probes (Table 1), as indicated by significant main effects of Task [$F(1,31)=20.81, p<0.0001$] and Probe [$F(1,31) = 8.97, p=0.005$].

In contrast, the two groups did not differ in their RTs to the memory probe [$F(1,31)=1.44$, $p=.24$], nor did Group interact with Task ($p=.19$), Set Size ($p=.16$), or Probe ($p=.45$). Instead, significant main effects of Task [$F(1,31)=42.69$, $p<0.0001$], Set Size [$F(1,31)=120.80$, $p<0.0001$], and Probe [$F(1,31) = 5.90$, $p=0.02$] were observed (Table 1). Responses were faster in the single task than in the dual task, faster for load 1 than for load 4, and faster for old probes than for new probes.

Associations between education level, self report questionnaires and accuracy performance in the dual task condition were determined using Spearman Rank Correlations (corrected at $p<.01$). Only scores on the BDI were related to accuracy scores to a marginally significant extent ($\rho=-0.463$, $p=0.008$). The correlation between PCL scores and accuracy did not reach significance ($\rho=-0.348$, $p=0.05$). Education was not significantly correlated with accuracy ($\rho=0.196$, $p=0.282$).

ERP Results:

Beginning with the 300-400 ms window, large effects of Task began to emerge. ERPs were more positive in the dual task compared to the single task condition [$F(1, 31)=37.6$, $p<.001$]. This Task effect interacted with Electrode [$F(5, 155)=32.4$, $p<.001$], being largest at Cz and FCz. Further, ERPs to old probes were more positive in amplitude than those to new probes [$F(1, 31)=9.6$, $p=.004$]. This Probe effect interacted with Task and Electrode [$F(5, 155)=2.8$, $p=.05$], such that Probe effects were larger at Cz and FCz in the single task, but were more uniform in the dual task. Finally, the analysis including the factor Set Size confirmed that ERPs to load 1 were more positive than those to load 4 [$F(1, 31)=6.2$, $p=.02$]. This Set Size effect interacted with Electrode [$F(5, 155)=3.5$, $p=.03$], being largest at Fz.

Of greatest interest was a three-way interaction between Task, Probe, and Group [$F(1, 31)=12.3, p=.001$]. This interaction was explored in follow up analyses conducted separately on the single and dual task conditions. For the single task alone, a strong effect of Probe was observed [$F(1, 31)=12.5, p=.001$], with more positive measurements for old probes. This effect did not interact with Group for the single task [$p=.36$] (See Figure 2 and 3). For the dual task alone, a main effect of Probe [$F(1, 31)=4.0, p=.05$] interacted with Group [$F(1, 31)=5.3, p=.03$]. This interaction was in turn followed up in separate analyses for each Group, which showed that, in the dual task condition, controls demonstrated a significant effect of Probe [$F(1, 15)=7.6, p=.02$], consistent with single task performance where old probes produced a more positive shift in the waveform (see Figure 2). However, individuals with PTSD did not show any distinction between old and new probes in the dual task condition [$p=.81$] (see Figure 3).

Largely similar effects and interactions were observed for the 400-500, 500-600, and 600-700 ms window, as shown in Table 2. The main effect of Task, and its interaction with Electrode, remained significant across all the later time windows. The critical interaction between Task, Probe, and Group remained significant through 600 ms, after which it reduced to a trend (see Table 2). Follow-up analyses demonstrated a consistent pattern, such that the interaction was driven by the performance of the PTSD group, who demonstrated a statistically flat effect of Probe during the dual task condition.

To correlate the magnitude of the Probe effects in the ERP data to self report measures, we calculated the average difference (old probes minus new probes) between 300-400 ms in the dual task condition. Spearman Rank Correlations (corrected at $p<.01$) found marginal effects of PCL scores impacting the difference between processing old and new probes in the ERP waveform ($\rho = -0.365, p=0.04$). When all the subscales of the PCL were entered into the

correlation matrix, only re-experiencing was significantly related to ERP processing differences in the dual task condition for old/new probes ($\rho = -.536, p=0.002$). Education and BDI scores were not significantly related to the ERP component.

Discussion

Both behavioral performance and electrophysiological changes support limited executive resources in PTSD patients. Patients with PTSD showed no significant WM impairment when performing the task alone. In the single task condition, PTSD patients performed similarly to military controls and showed similar patterns of electrophysiological components recognizing old and new probes. However, the addition of a difficult, secondary task caused significant changes in WM performance. PTSD patients declined significantly in responding accurately to probes and no longer showed any electrophysiological distinction between old and new probes. In addition, the deficits cannot be attributed to task difficulty since there was no interaction with the number of items to be remembered (1 or 4), suggesting that the impairment found in PTSD is related to coordinating task performance and not from a general decline in WM performance. Our findings suggest that dual task performance exacerbates WM difficulties found in PTSD patients.

As per Baddeley's model of WM (1996), the deficits found in the current task suggest limited CES in PTSD patients contributes to the poor performance in the dual task condition. Baddeley (1996) proposed that limited CES was linked to patients that typically showed behavioral difficulties with concentration, inhibition and attention. The patients with this reported behavioral dysfunction also showed the greatest impairment when multitasking. Baddeley (1996) suggests that the CES is associated with disorganized behavior often found in

patients with frontal lobe damage. Our current findings are similar to patients with frontal lobe damage that show CES deficits through impaired multitasking performance compared to performance on single tasks (McDowell et al., 1997). The behavioral performance in the current task replicates the association previously found with behavioral dysfunction and dual task performance (Baddeley, 1996).

Interestingly, the increase in errors was significantly correlated with the BDI self report measure of depression. Major depressive disorder has also been associated with WM deficits (Merriam et al., 1999; Pelosi et al., 2000; Sweeney et al., 1998) and some authors suggest that deficits in encoding strategies may be specifically related to depressive symptoms and not unique to patients with PTSD (Johnsen & Asbjornsen, 2008). Separating the effects of PTSD and depression on cognitive performance has not been a straightforward endeavor. In some cases, almost 50% of all PTSD patients report comorbid depression symptoms (Shalev et al., 1998). Unfortunately, it is unclear if the findings from the current study support accuracy impairment in coordinating WM tasks to depression or PTSD. Future studies incorporating a comparison group of depressive disorder without PTSD is needed to fully disentangle the effects of PTSD and depression.

In addition to performance, recognition of old and new probe items showed a significant group difference in the ERP waveform under the more difficult dual task conditions. Recognition of an item previously encoded compared to an item that was not previously encoded can be reflected in the ERP waveform starting around 400 ms (Johnson, Kreiter, Russo & Zhu, 1998). Both the PTSD group and the controls showed similar ERP effects from 300 ms to 500 ms when differentiating old and new probes in the single task condition, similar to previous reports on the ERP old/new effect (Rugg & Curran, 2007). However, when taxed with an

additional flanker task during the maintenance period, the PTSD group no longer produced any differentiating ERP pattern between old and new probes. The lack of differentiation reflects impaired performance in recognizing items under more difficult conditions.

Previous findings suggests that patients with PTSD use a passive recall strategy to echo the last few items on a list as indicated by an increase in recency scores on memory tests (Johnsen & Asbjornsen, 2009). If patients with PTSD use passive encoding strategies then it could be argued that the introduction of a secondary task would eliminate the ability to rehearse the encoded information. The neurophysiological difference in encoding old/new probes was significantly related to re-experiencing symptoms. This correlation supports previous theories suggesting that re-experiencing symptoms can cause deficits in learning and memory due to an inability to disengage from trauma-related memories, even on neutral, non-trauma related tasks (Vasterling et al., 1998).

This study has several limitations. We were unable to match the two groups for education, as has been reported in other studies (Swick et al., 2012). However, correlation and regression analyses showed no effect of education on any significant differences between groups in the working memory task. In addition, previous work with an expansion of this population showed no significant differences related to education or intelligence (see Swick et al., 2012). Another limitation is the lack of a neutral distraction task where participants only passively viewed flanker stimuli in between the set presentation and the probe.

Conclusion

Impairments in executive function have great clinical importance since even subtle deficits could influence coping style and cognitive reappraisal strategies (Vasterling & Verfaellie, 2009). Limitations in executive processing may contribute to the inability of

individuals with PTSD to disengage from traumatic memories (re-experiencing) and to modulate emotional responses (hyperarousal). These in turn may lead to withdrawal from situations in which executive control is likely to fail (avoidance and numbing) (Aupperle et al., 2012). The deficit in multitasking may be a useful measure of “real-world” functioning and important in evaluating effectiveness of rehabilitation treatments.

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Table 1. Accuracy (percent correct \pm SEM) and reaction time (mean \pm SEM, in msec) for the controls and the participants with PTSD.

Accuracy

Single Task

<u>Load 1 old</u>	<u>Load 1 new</u>	<u>Load 4 old</u>	<u>Load 4 new</u>	
Controls	98.0 \pm 0.6	95.6 \pm 1.3	97.4 \pm 1.0	94.5 \pm 1.1
PTSD	93.9 \pm 1.8	92.7 \pm 2.8	97.1 \pm 1.3	91.1 \pm 1.9

Dual Task

	<u>Load 1 old</u>	<u>Load 1 new</u>	<u>Load 4 old</u>	<u>Load 4 new</u>
Controls	96.6 \pm 1.3	93.4 \pm 2.0	95.0 \pm 1.4	90.6 \pm 1.4
PTSD	90.2 \pm 3.7	86.1 \pm 3.3	89.3 \pm 2.5	81.3 \pm 3.8

Reaction Time

Single Task

<u>Load 1 old</u>	<u>Load 1 new</u>	<u>Load 4 old</u>	<u>Load 4 new</u>	
Controls	769 \pm 46	882 \pm 60	1049 \pm 60	1135 \pm 95
PTSD	978 \pm 82	1102 \pm 91	1216 \pm 84	1210 \pm 85

Dual Task

	<u>Load 1 old</u>	<u>Load 1 new</u>	<u>Load 4 old</u>	<u>Load 4 new</u>
Controls	1027 \pm 79	1119 \pm 73	1279 \pm 72	1360 \pm 92
PTSD	1141 \pm 91	1206 \pm 110	1391 \pm 87	1394 \pm 115

Table 2

	100-120 ms	300-400 ms	400-500 ms	500-600 ms	600-700 ms
Task	$F=5.1$, $p=.03$	$F=37.6$, $p<.001$	$F=64.6$, $p<.001$	$F=30.4$, $p<.001$	$F=15.8$, $p<.001$
Task x Electrode	n.s.	$F=32.4$, $p<.001$	$F=38.0$, $p<.001$	$F=14.6$, $p<.001$	$F=11.6$, $p=.001$
Probe	n.s.	$F=9.6$, $p=.004$	$F=5.2$, $p=.03$	n.s.	n.s.
Task x Probe	$F=7.5$, $p=.01$	n.s.	$F=7.3$, $p=.01$	n.s.	n.s.
Task x Probe x Electrode	n.s.	$F=2.8$, $p=.05$	$F=3.2$, $p=.03$	$F=2.5$, $p=.08$	n.s.
Set Size	n.s.	$F=6.2$, $p=.02$	$F=7.1$, $p=.01$	$F=3.1$, $p=.09$	$F=8.1$, $p=.008$
Set Size x Electrode	n.s.	$F=3.5$, $p=.005$	$F=4.1$, $p=.01$	n.s.	$F=2.7$, $p=.07$
Group	$F=4.4$, $p=.05$	n.s.	n.s.	n.s.	n.s.
Probe x Group	n.s.	n.s.	$F=3.2$, $p=.08$	$F=4.0$, $p=.05$	$F=5.2$, $p=.03$
Task x Probe x Group	n.s.	$F=12.3$, $p=.001$	$F=6.0$, $p=.02$	$F=5.0$, $p=.03$	$F=3.2$, $p=.08$
Probe, single task	$F=5.0$, $p=.03$	$F=12.5$, $p=.001$	$F=13.4$, $p=.001$	n.s.	n.s.
Probe x Group, single task	n.s.	n.s.	n.s.	n.s.	n.s.
Probe, dual task	n.s.	$F=4.0$, $p=.05$	n.s.	n.s.	n.s.
Probe x Group, dual task	n.s.	$F=5.3$, $p=.03$	$F=6.3$, $p=.02$	$F=7.9$, $p=.009$	$F=8.6$, $p=.006$
Probe, dual task, controls	--	$F=7.6$, $p=.02$	$F=5.1$, $p=.04$	$F=4.9$, $p=.04$	$F=5.8$, $p=.03$
Probe, dual task, PTSD	--	n.s.	n.s.	$F=3.2$, $p=.09$	$F=3.4$, $p=.08$

Figure Captions

Figure 1: Mean percent correct responses to Sternberg probe items, as a function of Task (single, dual) and Group (controls, PTSD). Individuals with PTSD were less accurate than controls were at classifying Sternberg probes as old vs. new, particularly for the dual task.

Figure 2: Event-related potentials time locked to the onset of the Sternberg probe item, as a function of Task (single, dual), Electrode (6 midline electrodes), Probe (old, new), and Group (controls, PTSD). The ERP old/new effect – the relatively positive shift for previously presented (old) probes that are correctly recognized, relative to new probes that are correctly rejected – was observed beginning at 300 ms for both groups in the single task condition, but only for the controls in the dual task condition.

Figure 3: Topographic plots illustrating the old-new difference wave as a function of Task (single, dual) and Group (controls, PTSD). More positive measurements for previously presented (old) probes, relative to new probes, are indicated by warmer colors.

Figure 1

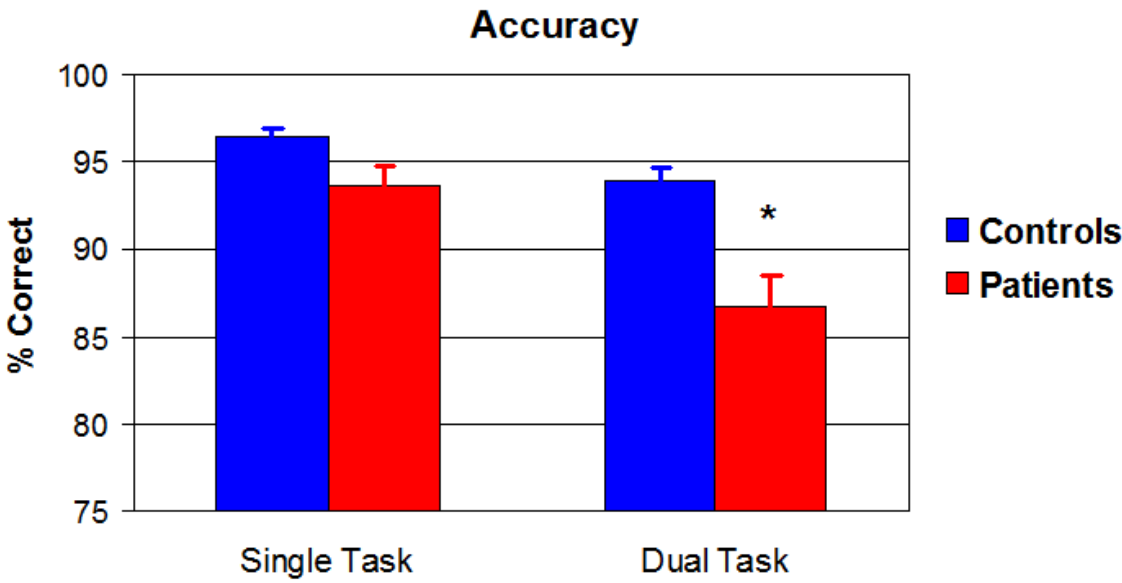


Figure 2

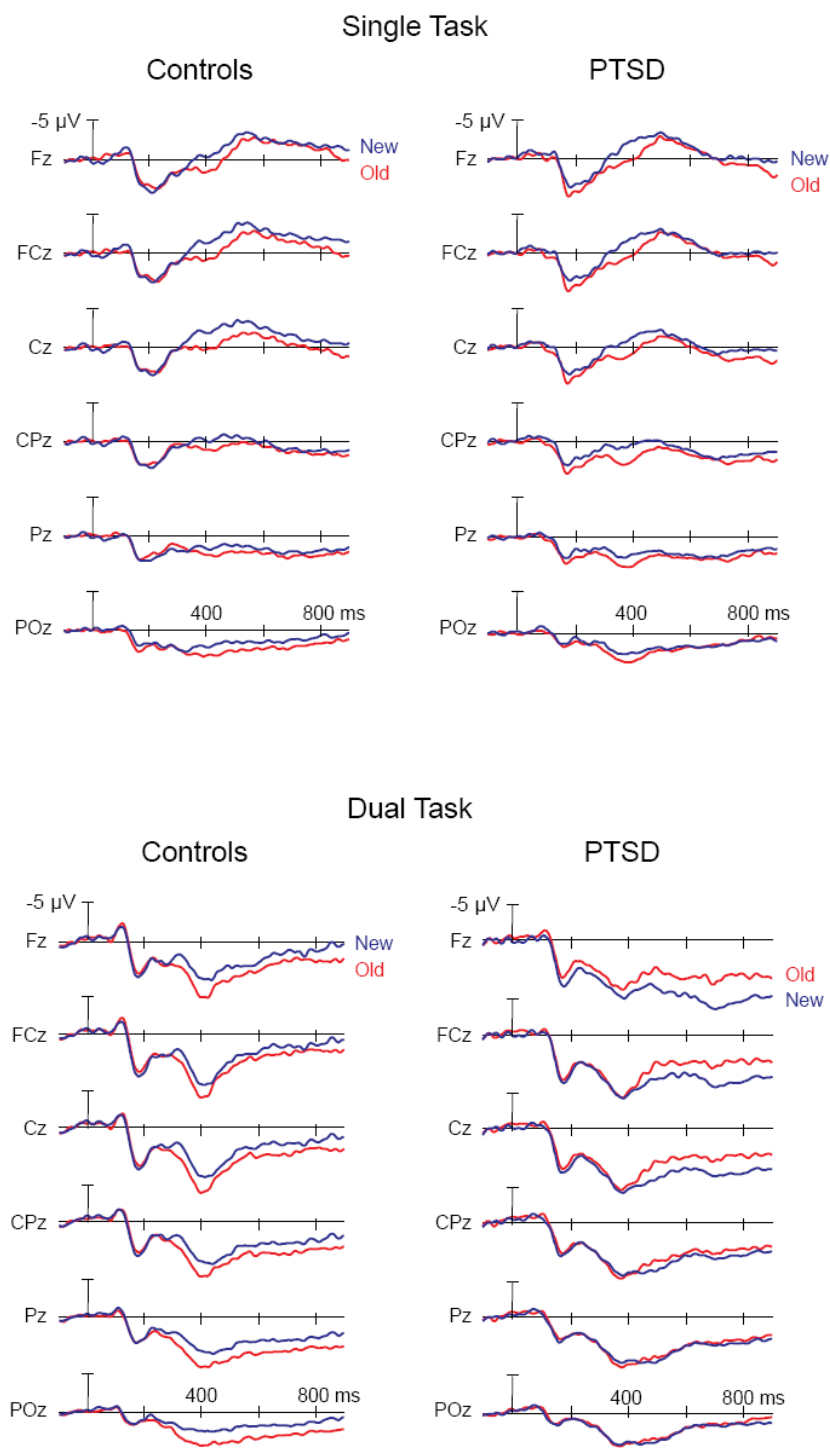
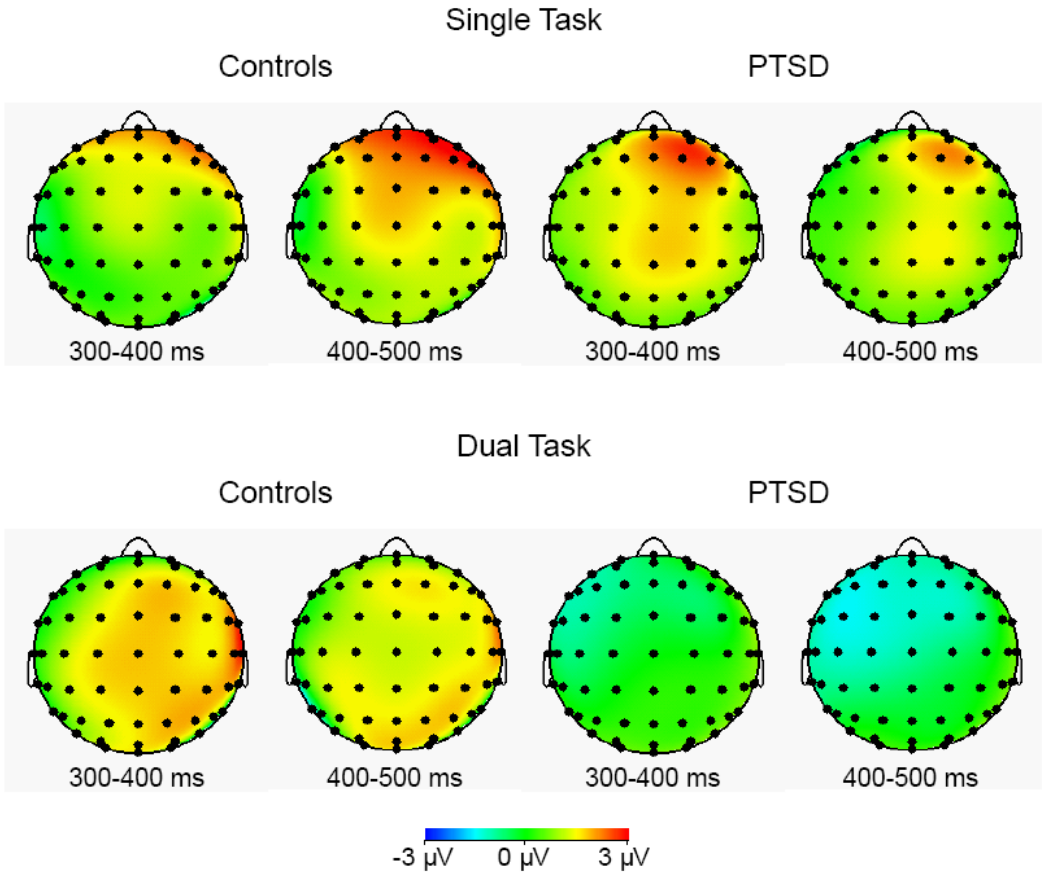


Figure 3





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Poster Abstract

Poster I4, Tuesday, April 3, 3:00 – 5:00 pm, 4th Floor Exhibit Hall

Impaired identification of facial expressions of fear in Iraq war veterans with PTSD and mTBI

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Studies suggest that patients with post-traumatic stress disorder (PTSD) process emotional facial expressions differently than healthy individuals; PTSD patients display exaggerated amygdala and diminished prefrontal cortex responses to fearful facial expressions. A recent study also found specific accuracy impairments and decreased sensitivity in recognizing expressions of fear and sadness in war veterans with PTSD (Poljac et al., 2011). To assess the role of PTSD in facial expression recognition, we showed pictures of faces to Iraq war veterans with PTSD and mild traumatic brain injury (mTBI), and to healthy age-matched military controls, and asked them to identify the expressions. A total of 140 faces (Ekman & Friesen, 1976) were presented in black and white, one at a time, in pseudo-randomized order. Faces had one of six basic expressions (happy, angry, fear, surprise sad, disgust) or neutral, with half of the expressions at 100% full intensity and the other half at 50% intensity made by morphing expressions with neutral (Calder, et al., 1996). Preliminary results suggest that, like Poljac et al. (2011), PTSD patients show impaired accuracy at identifying 50% intensity fear faces, relative to military controls ($p < .05$; Accuracy: patients=38%, controls=51%) and display a trend for impaired accuracy for full intensity fear faces ($p < .06$). PTSD patients also show a trend for misidentifying fear as surprise ($p < .1$). Our study did not find impairments on expressions of sadness, but is consistent with a growing body of research indicating altered processing of fearful facial expressions in PTSD (Poljac et al., 2011; Beevers et al., 2011).

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